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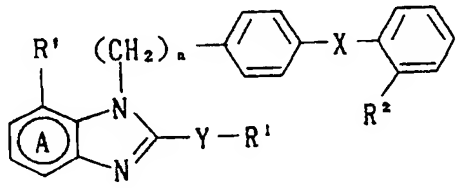
(54) Benzimidazole derivatives, their production and use.

(57) Benzimidazole derivatives of the formula (I):



(I)

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof, an amide thereof or a group capable of forming an anion or convertible to an anion; Y is -O-, $-S(O)_m-$ or $-N(R^4)-$ wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; and the pharmaceutically acceptable salts thereof, have potent angiotensin II antagonistic activity and antihypertensive activity, thus being useful as therapeutic agents for treating circulatory system diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, nephritis, etc.

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FIELD OF THE INVENTION

The present invention relates to novel benzimidazole derivatives having potent pharmacological actions and intermediates for the preparation thereof. More particularly, the present invention relates to compounds having potent anti-hypertensive activity and strong angiotensin II antagonistic activity, which are useful as therapeutic agents for treating circulatory diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, nephritis, etc.

BACKGROUND OF THE INVENTION

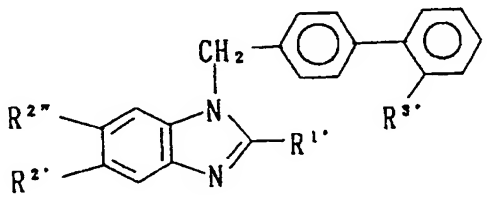
The renin-angiotensin system is involved in the homeostatic function to control systemic blood pressure, the volume of body fluid, balance among the electrolytes, etc., associated with the aldosterone system. Development of angiotensin II converting enzyme inhibitors (ACE inhibitor) (this converting enzyme produces angiotensin II which possesses a strong vasoconstrictive action) has clarified the relation between the renin-angiotensin system and hypertension. Since angiotensin II constricts blood vessel to elevate blood pressure via the angiotensin II receptors on the cellular membranes, angiotensin II antagonists, like the ACE inhibitor, would be useful in treating hypertension caused by angiotensin.

It has been reported that various angiotensin II analogues such as saralasin, [Sar^1 ,Ile^8]A II, and the like, possess potent angiotensin II antagonist activity.

It has, however, been reported that, when peptide antagonists are administered parenterally, their actions are not prolonged and, when administered orally, they are ineffective (M. A. Ondetti and D. W. Cushman, Annual Reports in Medicinal Chemistry, 13, 82-91 (1978)).

It would be highly desirable to develop a non-peptide angiotensin II antagonist which overcomes these drawbacks. In the earliest studies in this field, imidazole derivatives having angiotensin II antagonist activity have been disclosed in Japanese Patent Laid Open No. 71073/1981; No. 71074/1981; No. 92270/1982; No. 157768/1983; USP No. 4,355,040, No. 4,355,040, etc. Later, improved imidazole derivatives are disclosed in European Patent Laid Open No. 0253310, No. 0291969, No. 0324377, Japanese Patent Laid Open No. 23868/1988; and No. 117876/1989. Further, pyrole, pyrazole, and triazole derivatives are disclosed as angiotensin II antagonists in European Patent Laid Open No. 0323841, and Japanese Patent Laid Open No. 287071/1989.

USP No. 4,880,804 discloses benzimidazole derivatives having an angiotensin II receptor antagonistic action, which are intravenously active in vivo in rats with renal hypertension. Examples of such benzimidazole derivatives are those represented by the following formula (A):



(A)

wherein substituents, for example, in the 5- and/or 6-position are hydroxymethyl, methoxy, formyl, chloro, or carboxy. Although most compounds among those exemplified are orally inactive, it is said that only the 6-hydroxymethyl and 6-chloro compounds are orally effective (100 mg/kg or less). It is, however, believed that the activity of even these disclosed compounds is insufficient for clinical uses.

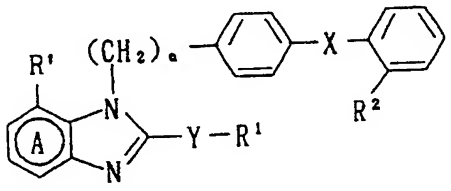
SUMMARY OF THE INVENTION

The present invention provides novel benzimidazole derivatives having potent anti-hypertensive activity and strong angiotensin II antagonistic action, which are of practical value in clinical use as therapeutic agents.

The present inventors considered that compounds functioning to control the renin-angiotensin system as well as clinically useful for the treatment of circulatory diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, etc. are required to have potent angiotensin II receptor antagonistic activity and to exert strong oral and long-lasting angiotensin II antagonist action. Extensive investigations were made based on those consideration. As a

result of this research, the present inventors have succeeded in synthesizing novel 2-substituted benzimidazole derivatives (I) possessing highly angiotensin II receptor antagonistic activity as well as exerting strong oral and long-lasting angiotensin II antagonistic and anti-hypertensive action and developed the present invention.

The present invention relates to benzimidazole derivatives having the formula I:



(I)

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof, an amide thereof or a group capable of forming an anion or convertible to an anion; Y is -O-, $-S(O)_m-$ or $-N(R^4)-$ wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; and the pharmaceutically acceptable salts thereof.

These compounds are unexpectedly potent angiotensin II antagonists which are of value in the treatment of circulatory system diseases such as hypertensive diseases, heart diseases, strokes, nephritis, etc.

Another aspect of the present invention relates to pharmaceutical compositions comprising an effective amount of the benzimidazole derivative having the formula I and a pharmaceutically acceptable carrier useful in treating circulatory system diseases such as hypertensive diseases, heart diseases, strokes, renal failure, nephritis, etc., and processes for preparing such compounds and compositions.

Still another aspect of the present invention relates to a method for treating said circulatory system diseases of animals, which comprises administering an effective amount of the benzimidazole derivatives having the formula I or the pharmaceutical composition thereof to said animal.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a X ray scattering chart obtained in Experimental Example 1.

FIG. 2 depicts an IR spectrum pattern obtained in Experimental Example 1.

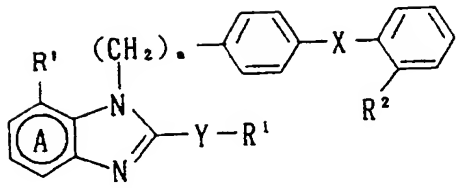
FIG. 3 depicts a differential scanning calorimeter pattern obtained in Experimental Example 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the benzimidazole derivatives (I) and the pharmaceutically acceptable salts thereof, which possess strong angiotensin II antagonist activity and are of value in the treatment of circulatory diseases such as hypertensive diseases, heart diseases, strokes, cerebral diseases, nephritis, etc., pharmaceutical compositions comprising an effective amount of the benzimidazole derivative having the formula I and a pharmaceutically acceptable carrier useful in treating said circulatory diseases, and processes for preparing such compounds and compositions.

The present invention further provides a method for treating said circulatory system diseases of animals, which comprises administering an effective amount of the benzimidazole derivative (I) or the pharmaceutical composition thereof to said animal.

An important group of compounds according to the present invention are the compounds of the formula I":



(I")

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof or an amide thereof ; Y is -O-, $-S(O)_m-$ or $-N(R^4)-$wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; and the pharmaceutically acceptable salts thereof.

With regard to the foregoing formula (I), hydrocarbon residues for R^1 include, for example, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and aralkyl groups. Among them, alkyl, alkenyl, and cycloalkyl groups are preferable.

Alkyl groups for R^1 are lower alkyl groups having 1 to about 8 carbon atoms, which may be straight or branched, and include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like.

Alkenyl groups for R^1 are lower alkenyl groups having 2 to about 8 carbon atoms, which may be straight or branched, and include, for example, vinyl, propenyl, 2-butenyl, 3-butenyl, isobutenyl, octenyl, and the like.

Alkynyl groups for R^1 are lower alkynyl groups having 2 to about 8 carbon atoms, which may be straight or branched, and include, for example, ethynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 2-octynyl, and the like.

Cycloalkyl groups for R^1 are lower cycloalkyl groups having 3 to about 6 carbon atoms, and include, for example, cyclopropyl, cyclobutyl, cyclopentyl, and the like.

The above-mentioned alkyl, alkenyl, alkynyl, and cycloalkyl groups may be substituted with hydroxyl, an optionally substituted amino group (e.g. amino, methylamino, etc.), halogen, a lower (C_{1-4}) alkoxy group or the like.

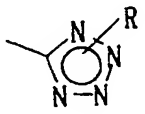
Aralkyl groups for R^1 include, for example, phenyl-lower (C_{1-4}) alkyl such as benzyl, phenethyl, and the like, and the aralkyl group may be substituted with, for example, halogen (e.g. F, Cl, Br, etc.), nitro, lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, etc.), lower (C_{1-4}) alkyl (e.g. methyl, ethyl, etc.), or the like at various positions of the benzene ring.

Aryl groups for R^1 include, for example, phenyl and the aryl group may be substituted with, for example, halogen (e.g. F, Cl, Br, etc.), nitro, lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, etc.), lower (C_{1-4}) alkyl (e.g. methyl, ethyl, etc.), or the like at various positions of the benzene ring.

Among the above-mentioned groups for R^1, preferred examples are optionally substituted alkyl and alkenyl groups (e.g. lower (C_{1-5}) alkyl and lower (C_{2-5}) alkenyl groups optionally substituted with hydroxyl, an amino group, halogen or a lower (C_{1-4}) alkoxy group).

Examples of groups capable of forming an anion and groups convertible thereinto for R^2 include carboxyl, tetrazolyl, trifluoromethanesulfonic amide ($-NHSO_2CF_3$), phosphoric acid, sulfonic acid, cyano, lower (C_{1-4}) alkoxycarbonyl, and the like. These groups may be protected with, for example, an optionally substituted lower alkyl group (e.g. lower (C_{1-4}) alkoxymethyl, optionally substituted arylmethyl, etc.) or an acyl group (e.g. lower (C_{2-5}) alkanoyl, optionally substituted benzoyl, etc.). Such groups may include those which are capable of forming anions or convertible thereinto either chemically or under biological and/or physiological conditions (for example, in vivo reaction such as oxidation-reduction or hydrolysis catalyzed by in vivo enzymes).

The compounds wherein R^2 is a group capable of forming an anion or convertible thereinto chemically (e.g. by oxidation, reduction or hydrolysis) (for example, an optionally protected tetrazolyl group (e.g. a group having the formula:



wherein R is methyl, triphenylmethyl, 2-tetrahydropyranyl, tert-butyl, methoxymethyl, ethoxymethyl, or optionally substituted benzyl such as p-methoxybenzyl and p-nitrobenzyl), cyano and the like), are useful as synthetic intermediates.

Among the above-mentioned groups for R^2, preferred examples are tetrazolyl groups optionally protected with optionally substituted lower alkyl or acyl, carboxyl groups optionally protected with optionally substituted lower alkyl, and trifluoromethanesulfonic amide.

Examples of carboxyl, esters thereof or amides thereof for R' include, for example, groups having the formula: -CO-D' wherein D' is hydroxyl, optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkylamino, N,N-dilower (C_{1-4}) alkyl amino, etc.), or optionally substituted alkoxy [e.g. lower (C_{1-6}) alkoxy optionally substituted with hydroxyl, optionally substituted amino (e.g. amino, dimethylamino, diethylamino, piperidino, morpholino, etc.), halogen, lower (C_{1-6}) alkoxy, lower (C_{1-6}) alkylthio or optionally substituted dioxolenyl (e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl, etc.) on the alkyl moiety and groups having the formula: -OCH(R^7)-OCOR^8 wherein R^7 is hydrogen, straight or branched lower alkyl having 1 to 6 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.), or cycloalkyl having 5 to 7 carbon atoms (e.g. cyclopentyl, cyclohexyl, cycloheptyl, etc.) and R^8 is straight or branched lower alkyl having 1 to 6 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.), straight or branched lower alkenyl having 2 to about 8 carbon atoms (e.g. vinyl, propenyl, 2-butenyl, 3-butenyl, isobutenyl, octenyl, etc.), cycloalkyl having 5 to 7 carbon atoms (e.g. cyclopentyl, cyclohexyl, cycloheptyl, etc.), lower (C_{1-3}) alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. benzyl, p-chlorobenzyl, phenethyl, cyclopentylmethyl, cyclohexylmethyl, etc.), lower (C_{2-3}) alkenyl (e.g. vinyl, propenyl, allyl, isopropenyl, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. cinnamyl, etc.), optionally substituted aryl (e.g. phenyl, p-tolyl, naphthyl, etc.), straight or branched lower alkoxy having 1 to 6 carbon atoms (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, n-pentyloxy, isopentyloxy, neopentyloxy, etc.), straight or branched lower alkenyloxy having 2 to about 8 carbon atoms (e.g. allyloxy, isobutenyloxy, etc.), cycloalkyloxy having 5 to 7 carbon atoms (e.g. cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, etc.), lower (C_{1-3}) alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. benzyloxy, phenethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, etc.), lower (C_{2-3}) alkenyloxy (e.g. vinyloxy, propenyloxy, allyloxy, isopropenyloxy, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. cinnamyloxy, etc.), optionally substituted aryloxy (e.g. phenoxy, p-nitrophenoxy, naphthoxy, etc.)]. Examples of groups capable of forming an anion and groups convertible thereinto for R' may include, for example, tetrazolyl groups optionally protected with optionally substituted lower alkyl such as lower (C_{1-4}) alkyl and lower (C_{1-4}) alkoxy lower (C_{1-4}) alkyl or acyl such as lower (C_{2-5}) alkanoyl and optionally substituted benzoyl, trifluoromethanesulfonic amide, phosphoric acid, sulfonic acid, and the like. Examples of substituents for R' include -COOH and salts thereof, -COOMe, -COOEt, -COOtBu, -COOPr, pivaloyloxymethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyloxycarbonyl, acetoxymethyloxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxycarbonyl, isobutyryloxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl, 1-(acetyloxy)ethoxycarbonyl, 1-(isobutyryloxy)ethoxycarbonyl, cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, cinnamyloxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl, etc. Such groups may include those which are capable of forming anions (e.g. -COO-, derivatives thereof, etc.) or convertible thereinto either chemically or under biological and/or physiological conditions (for example, in vivo reaction such as oxidation-reduction or hydrolysis catalyzed by in vivo enzymes).

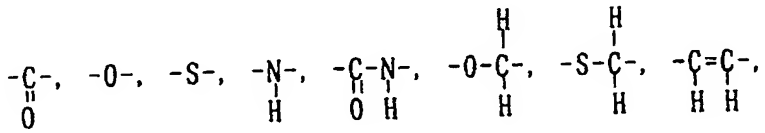
The benzene ring $\overline{A}$ may optionally contain substitution in addition to the R' group and such substituents include halogen (e.g. F, Cl, Br, etc.); nitro; cyano; optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkyl such as methylamino and ethylamino, N,N-dilower (C_{1-4}) alkyl amino such as dimethylamino and diethylamino, N-arylamino such as phenylamino and naphthylamino, N-aralkylamino such as benzylamino and naphthylmethylamino, and alicyclic amino such as morpholino, piperidino, piperazino and N-phenylpiperazino]; groups having the formula: -W-R^{13} wherein W is a chemical bond, -O-, -S-, or

$$-\overset{\overset{O}{\|}}{C}-,$$

and R^{13} is hydrogen or an optionally substituted lower alkyl group (e.g. lower (C_{1-4}) alkyl optionally substituted with hydroxyl, optionally substituted amino (e.g. amino, dimethylamino, diethylamino, piperidino, morpholino, etc.), halogen or lower (C_{1-4}) alkoxy, etc.); groups having the formula: $-(CH_2)_p$-CO-D wherein D is hydrogen, hydroxyl, optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkylamino, N,N-dilower (C_{1-4}) alkyl amino, etc.), or optionally substituted alkoxy [e.g. lower (C_{1-6}) alkoxy optionally substituted with hydroxyl, optionally substituted amino (e.g. amino, dimethylamino, diethylamino, piperidino, morpholino, etc.), halogen, lower (C_{1-6}) alkoxy, lower (C_{1-6}) alkylthio or optionally substituted dioxolenyl (e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl, etc.) on the alkyl moiety and groups having the formula: $-OCH(R^9)OCOR^{10}$ wherein R^9 is hydrogen, straight or branched lower alkyl having 1 to 6 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.), or cycloalkyl having 5 to 7 carbon atoms (e.g. cyclopentyl, cyclohexyl, cycloheptyl, etc.) and R^{10} is straight or branched lower alkyl having 1 to 6 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.), straight or branched lower alkenyl having 2 to about 8 carbon atoms (e.g. vinyl, propenyl, 2-butenyl, 3-butenyl, isobutenyl, octenyl, etc.), cycloalkyl having 5 to 7 carbon atoms (e.g. cyclopentyl, cyclohexyl, cycloheptyl, etc.), lower (C_{1-3}) alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. benzyl, p-chlorobenzyl, phenethyl, cyclopentylmethyl, cyclohexylmethyl, etc.), lower (C_{2-3}) alkenyl (e.g. vinyl, propenyl, allyl, isopropenyl, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. cinnamyl, etc.), optionally substituted aryl (e.g. phenyl, p-toluyl, naphthyl, etc.), straight or branched lower alkoxy having 1 to 6 carbon atoms (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, n-pentyloxy, isopentyloxy, neopentyloxy, etc.), straight or branched lower alkenyloxy having 2 to about 8 carbon atoms (e.g. allyloxy, isobutenyloxy, etc.), cycloalkyloxy having 5 to 7 carbon atoms (e.g. cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, etc.), lower (C_{1-3}) alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. benzyloxy, phenethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, etc.), lower (C_{2-3}) alkenyloxy (e.g. vinyloxy, propenyloxy, allyloxy, isopropenyloxy, etc.) which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms (e.g. cinnamyloxy, etc.), optionally substituted aryloxy (e.g. phenoxy, p-nitrophenoxy, naphthoxy, etc.)], and p is 0 or 1; tetrazolyl optionally protected with, for example, an optionally substituted lower alkyl group (e.g. lower (C_{1-4}) alkoxymethyl, optionally substituted arylmethyl, etc.) or an acyl group (e.g. lower (C_{2-5}) alkanoyl, optionally substituted benzoyl, etc.); trifluoromethanesulfonic amide; phosphoric acid; sulfonic acid; etc.

One or two of these substituents may be substituted at various positions of the benzene ring. When two substituents are present at the 4 and 5 or 5 and 6 positions on the ring A, they may be taken together to form a ring (e.g. benzene, etc.). Such rings may be substituted with the same groups as for the ring A.

X shows that the adjacent phenylene group is bonded to the phenyl group directly or through a spacer with an atomic chain of 2 or less. As the spacer, any one can be exemplified, so long as it is a divalent chain in which the number of atoms constituting the straight chain is 1 or 2, and it may have a side chain. Examples of such spacers include lower (C_{1-4}) alkylene,



etc. The most preferred X is a chemical bond between the phenylene group and the phenyl group.

Y represents that R^1 is bonded to the 2-position of benzimidazole through a hetero atom. Examples of Y include -O-, $-SO_m$- wherein m is 0, 1, or 2, $-N(R^4)$- wherein R^4 is hydrogen or an optionally substituted lower (C_{1-4}) alkyl group, and the like, preferably -O-, -S-, and -NH-, more preferably -O- and -S-, especially -O-. R^1 and R^4 may be taken together with the N atom attached thereto to form a heterocyclic ring (e.g. piperidino, morpholino, etc.).

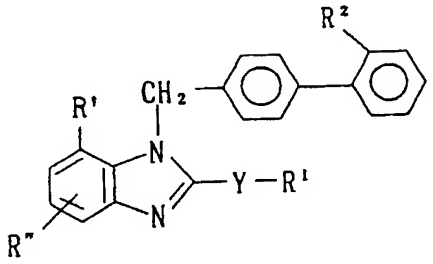
When R^1 = H, the compounds having the formula (I) [Compound (I)] can exist in two tautomeric forms.

When the compounds of the present invention have several asymetric carbon atoms, they can thus exist in several stereochemical forms. The invention includes the mixture of isomers and the individual stereoisomers. It is intended that the present invention includes geometrical isomers, rotational isomers, enantiomers, racemates, and diastereomers.

The compounds of the present invention can exist in any pro-drug form of those wherein R' is carboxyl

or the anion therefrom.

Among the compounds represented by the above formula (I), a preferred embodiment of the invention is a compound of the formula:

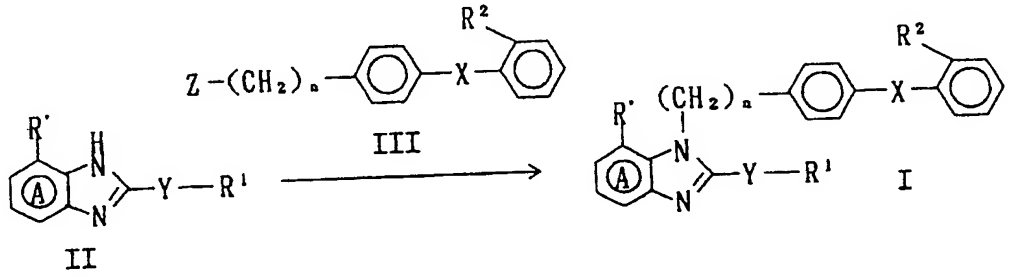


(I')

wherein R^1 is lower (C_{1-5}) alkyl optionally substituted with hydroxyl, amino, halogen, or a lower (C_{1-4}) alkoxy group (inter alia lower (C_{2-3}) alkyl); R' is -CO-D' wherein D' is hydroxyl, amino, N-lower (C_{1-4}) alkylamino, N,N-dilower (C_{1-4}) alkyl amino, or lower (C_{1-4}) alkoxy optionally substituted with hydroxyl, amino, halogen, lower (C_{1-4}) alkoxy, lower (C_{2-8}) alkanoyloxy (e.g. acetyloxy, pivaloyloxy, etc.) or 1-lower (C_{1-6}) alkoxycarbonyloxy (e. g. methoxycarbonyloxy, ethoxycarbonyloxy, cyclohexyloxycarbonyloxy, etc.) on the alkyl moiety, or tetrazolyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl or acyl group (e.g. lower (C_{2-5}) alkanoyl, benzoyl, etc.); R^2 is tetrazolyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl (e.g. methyl, triphenylmethyl (trityl), methoxymethyl, ethoxymethyl, p-methoxybenzyl, p-nitrobenzyl, etc.) or acyl group (e.g. lower (C_{2-5}) alkanoyl, benzoyl, etc.), or carboxyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl group (e.g. methyl, triphenylmethyl (trityl), methoxymethyl, ethoxymethyl, p-methoxybenzyl, p-nitrobenzyl, etc.); R'' is hydrogen, halogen, lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy, nitro or -CO-D'' wherein D'' is hydroxyl or lower (C_{1-2}) alkoxy optionally substituted with hydroxyl, lower (C_{1-4}) alkoxy, lower (C_{2-6}) alkanoyloxy (e.g. acetyloxy, pivaloyloxy, etc.) or 1-lower (C_{1-6}) alkoxycarbonyloxy (e. g. methoxycarbonyloxy, ethoxycarbonyloxy, cyclohexyloxycarbonyloxy, etc.) on the alkyl moiety, or amino optionally substituted with lower (C_{1-4}) alkyl (inter alia hydrogen, lower (C_{1-4}) alkyl, or halogen, more preferably hydrogen); and Y is -O-, -S-, or -N(R^4)- wherein R^4 is hydrogen or an lower (C_{1-4}) alkyl group; and the pharmaceutically acceptable salts thereof.

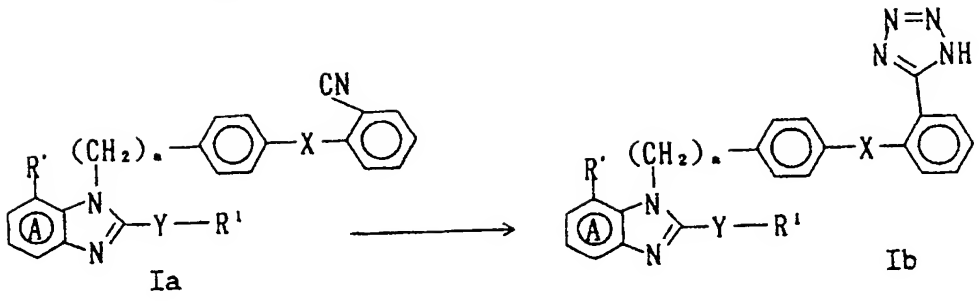
The compounds (I) of the present invention may be prepared by several reaction schemes, as illustrated below for a preferred compound.

Scheme A



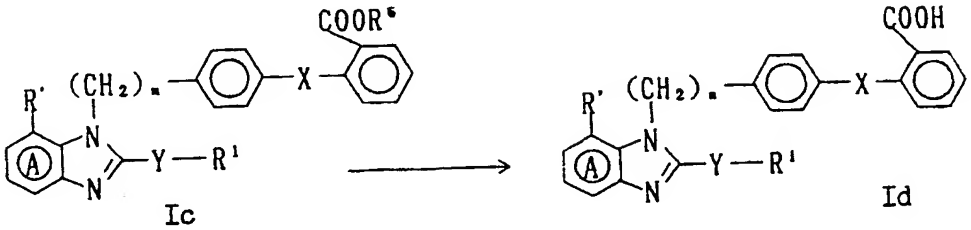
wherein R^1, R^2, R', A, X, Y and n have the above-defined meanings and Z is halogen.

Scheme B



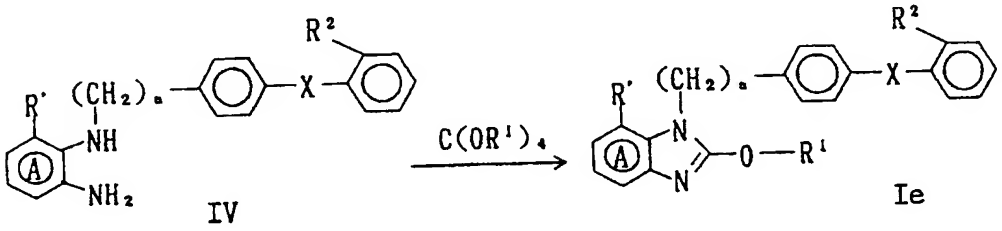
wherein each group has the above-defined meaning.

Scheme C



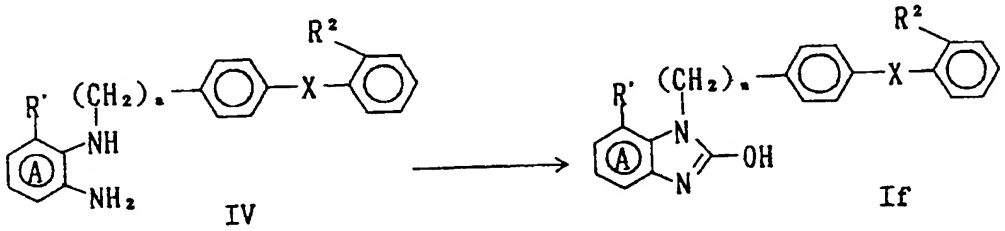
wherein R^1, R', A, X, Y and n have the above-defined meanings, and R^5 is optionally substituted lower (C_{1-6}) alkyl.

Scheme D



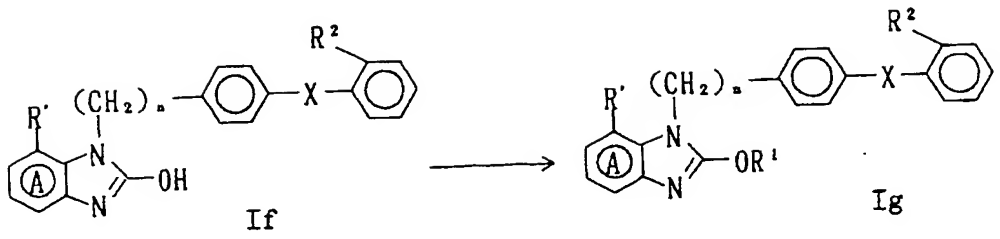
wherein each group has the above-defined meaning.

Scheme E



wherein each group has the above-defined meaning.

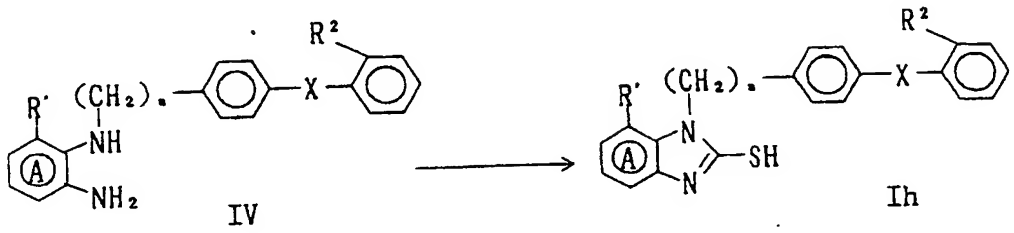
Scheme F



If Ig

wherein each group has the above-defined meaning.

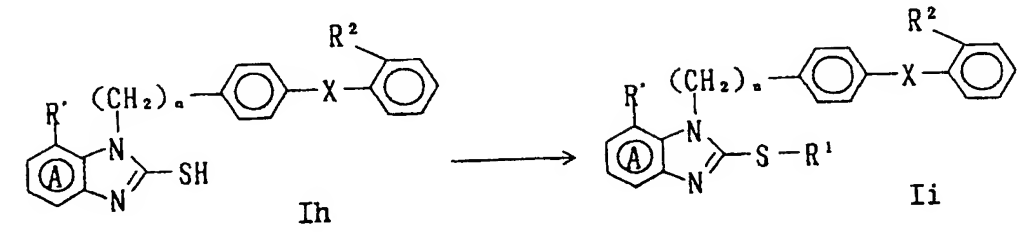
Scheme G



IV Ih

wherein each group has the above-defined meaning.

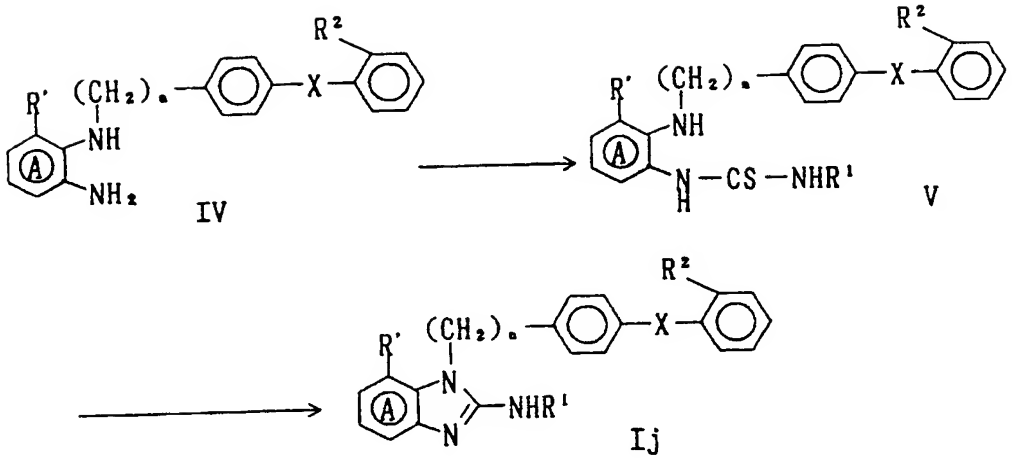
Scheme H



Ih Ii

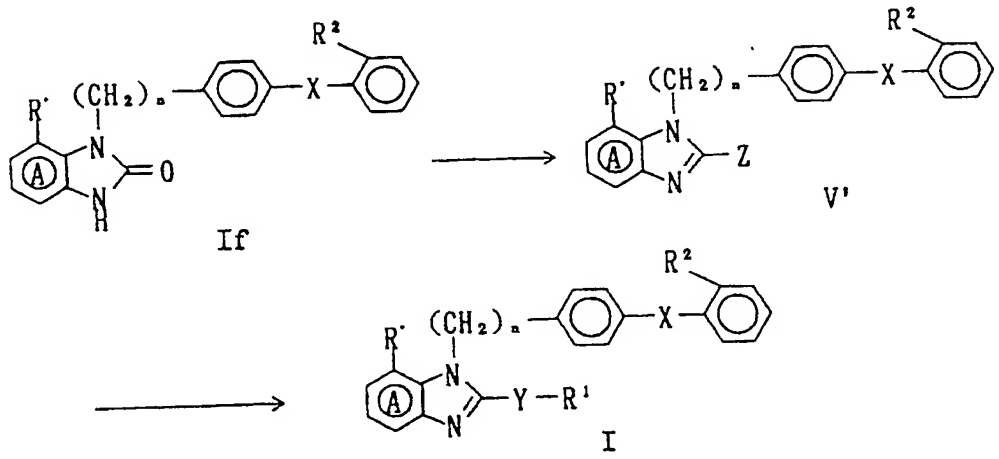
wherein each group has the above-defined meaning.

Scheme I



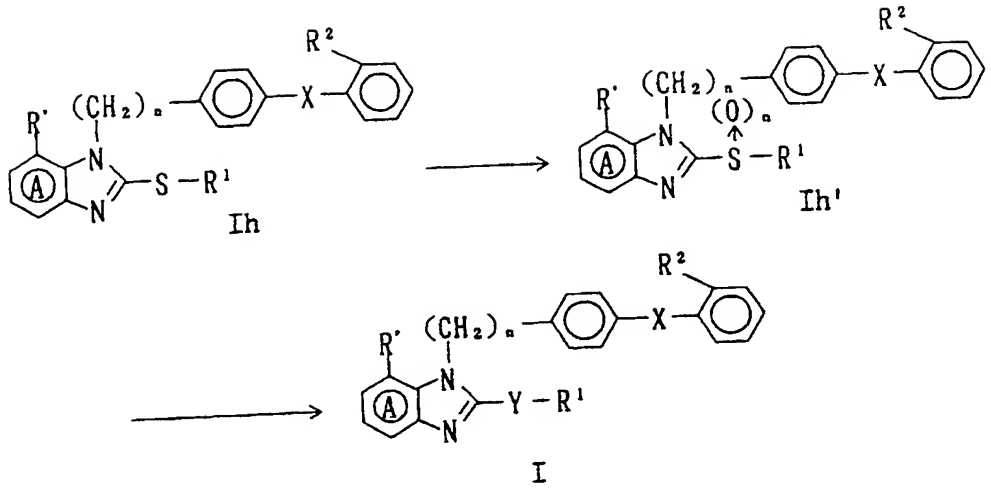
wherein each group has the above-defined meaning.

Scheme I'



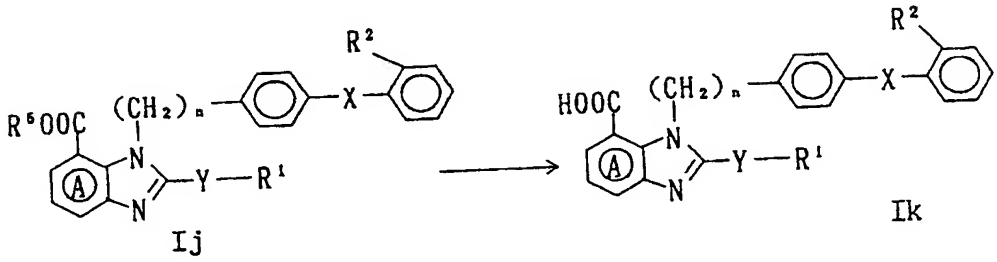
wherein each group has the above-defined meaning.

Scheme I''



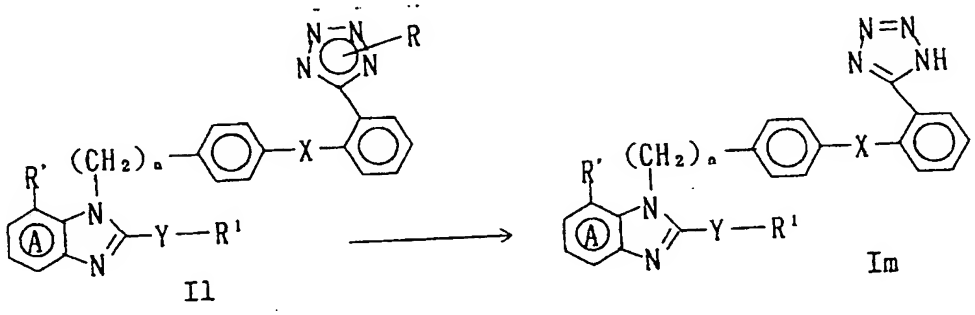
wherein each group has the above-defined meaning.

Scheme J



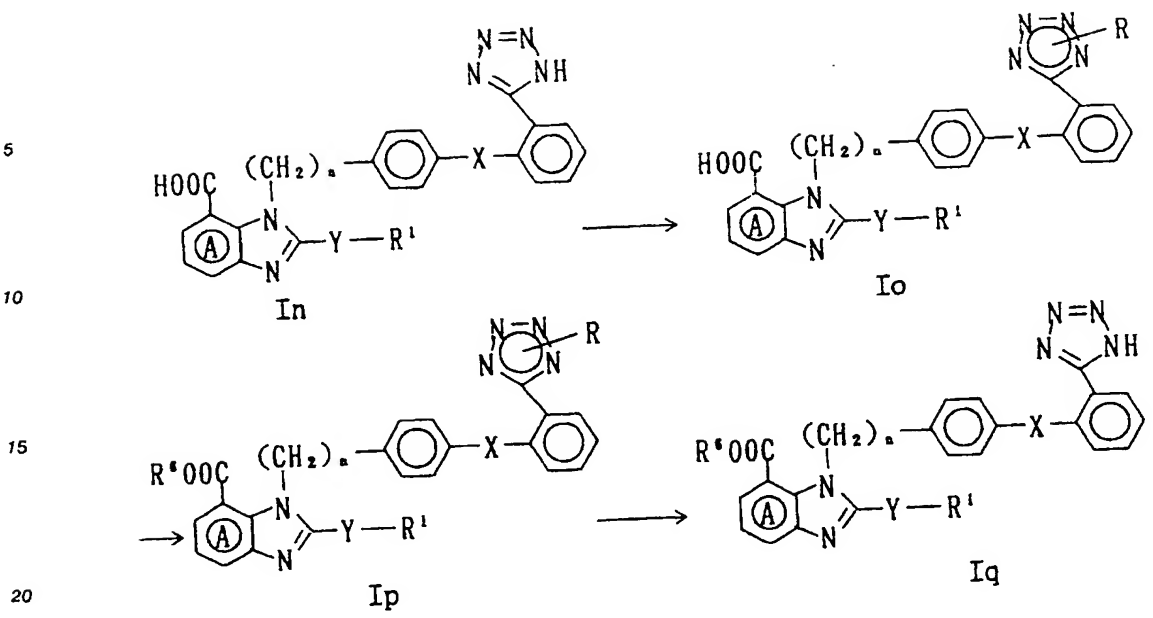
wherein each group has the above-defined meaning.

Scheme K



wherein each group has the above-defined meaning.

Scheme L



wherein A, R, R', X, Y and n have the above-defined meanings, and R^6 is lower (C_{1-6}) alkyl optionally substituted with lower (C_{2-6}) alkanoyloxy, 1-lower (C_{1-6}) alkoxycarbonyloxy or the like as defined for R'.

The reaction as illustrated in Scheme A is an alkylation using an alkylating agent in the presence of a base. One molar portion of the compound (II) is employed with approximately 1 to 3 moles of the base and 1 - 3 moles of the alkylating agent. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, tetrahydrofuran, acetone, ethylmethylketone, and the like. Examples of such bases include sodium hydride, potassium t-butoxide, potassium carbonate, sodium carbonate, and the like. Examples of such alkylating agents include substituted halides (e.g. chlorides, bromides, iodides, and the like), substituted sulfonate esters (e.g. p-toluenesulfonate esters, and the like), etc. The reaction conditions may vary depending on the combination of the base and the alkylating agent. Advantageously, the reaction is carried out at ice-cooling to room temperature for about 1 - 10 hours.

In the said alkylation, a mixture of two isomers, (I) and (I''') is usually obtained depending on the position of the N atom to be alkylated. While the production ratio of Compound (I) and Compound (I''') varies with the reaction conditions employed and the substituents on the benzimidazole ring, these two compounds can be obtained easily as pure products respectively by conventional isolation and/or purification methods (e.g. recrystallization, column chromatography and the like).

The nitrile compound (Ia) is reacted with various azides to form the tetrazole compound (Ib) as illustrated in Scheme B. One molar portion of the compound (Ia) is employed with 1 - 5 moles of the azide. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, toluene, benzene, and the like. Examples of such azides include trialkyltin azide (e.g. trimethyltin azide, tributyltin azide, triphenyltin azide, etc.), hydrogen azide and ammonium salts thereof, and the like. In the case where the organotin azide compound is employed, 1 - 4 moles of the azide are employed per compound (Ia) and the reaction is carried out in toluene or benzene by heating under reflux for a period of 1 - 4 days. When the hydrogen azide or its ammonium salt is used, 1 - 5 moles of sodium azide and ammonium chloride or tertiary amine (e.g. triethylamine, tributylamine, etc.) are employed per compound (Ia) and the reaction is conducted in dimethylformamide at about 100°C - 120°C for about 1 - 4 days. During this reaction, it is preferable to facilitate the reaction by adding an appropriate amount of sodium azide and ammonium chloride. In this case, improvement may sometimes be observed in reaction time and yield by the addition of the azide compound in suitable fractions.

The ester (Ic) is hydrolyzed in the presence of alkali to give the carboxylic acid (Id) as illustrated in Scheme C. This reaction is conducted usually in a solvent such as aqueous alcohol (e.g. methanol, ethanol, methyl cellosolve, etc.) by using alkali in an amount of about 1 to 3 mol. relative to 1 mol. of Compound (Ic). Examples of such alkalis include sodium hydroxide, potassium hydroxide, etc. The reaction is conducted at temperatures ranging from room temperature to about 100°C for about 1 to 10 hours,

preferably around the boiling point of the solvent for about 2 to 5 hours.

The 2-alkoxy derivative (Ie) is obtained by reacting phenylenediamine (IV) with alkyl orthocarbonate as illustrated in Scheme D. The reaction is conducted in the presence of an acid by using alkyl orthocarbonate of about 1 to 3 mol. relative to Compound (IV). Examples of such alkyl orthocarbonates include orthocarbonates of, for example, methyl, ethyl, propyl, isopropyl, butyl, etc. And, by using ,for example, acetic acid or p-toluenesulfonic acid, the reaction is accelerated to afford a ring-closed compound in a good yield. As the reaction solvent, halogenated hydrocarbons and ethers can be employed but, usually, it is more convenient to conduct the reaction without a solvent. The reaction is usually conducted at about 70 to 100°C for about 1 to 5 hours. In this reaction, a dialkoxyimino compound is produced as the reaction intermediate, which is then ring-closed into the 2-alkoxy compound (Ie) in the presence of the acid in the reaction system. It is also possible to isolate the reaction intermediate, which is then subjected to ring-closure reaction in the presence of an acid to form the 2-alkoxy compound (Ie).

The phenylenediamino compound (IV) is reacted with various reagents to give the 2-keto compound (or the 2-hydroxy compound, If) as illustrated in Scheme E. This reaction is conducted by using a carbonylating reagent (e.g. urea, diethyl carbonate, bis(1-imidazolyl)ketone, etc.) in an amount of about 1 to 5 mol. relative to 1 mol. of Compound (IV) and, usually, by using, among others, halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.), alcohols (e.g. methanol, ethanol, etc.) or amides (e.g. dimethylformamide, dimethylacetamide, etc.).

The 2-hydroxy compound (If) is selectively O-alkylated with a Meerwein reagent to give the 2-alkoxy compound (Ig) as illustrated in Scheme F. This reaction is conducted by using the Meerwein reagent in an amount of about 1 to 3 mol. relative to Compound (If), usually, employing, as the solvent, halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.) or ethers (e.g. methyl ether, ethyl ether, etc.). Examples of such Meerwein reagents include, among others, trimethyl oxonium fluoroborate ($Me_3O^+BF_4^-$), triethyl oxonium fluoroborate ($Et_3O^+BF_4^-$), etc. These are preferably used by in situ preparation according to the method described in literature references [H. Meerwein, Org. Syn. 46. 113 and 120(1966)]. The reaction is preferably conducted at temperatures ranging from about room temperatures to the boiling point of the solvent used for about 2 to 20 hours.

The phenylene diamino compound (IV) is reacted with various reagents in an organic solvent to give the 2-mercapto compound (Ih) as illustrated in Scheme G. Relative to 1 mol. of the phenylene diamino compound (IV), about 1 to 3 mol. of a thiocarbonylating agent (e.g. carbon disulfide, thiourea, potassium xanthate, etc.) or isothiocyanate (e.g. methyl isothiocyanate, ethyl isothiocyanate, etc.) is used. As the reaction solvent, alcohols (e.g. methanol, ethanol, etc.), amides (e.g. dimetylformamide, dimethylacetamide, etc.) or the like can be used. The reaction is preferably conducted at temperatures ranging from room temperatures to the boiling point of the solvent used for about 5 to 20 hours.

The 2-mercapto compound (Ih) is alkylated in the presence of a base in an organic solvent to give the alkylthio compound (Ii) as illustrated in Scheme H. The reaction is conducted by using, relative to 1 mol. of Compound (Ih), about 1 to 3 mol. of the base and about 1 to 3 mol. of the alkylating agent usually in a solvent such as dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, acetone, ethyl methyl ketone, ethanol, methanol and water. As the base, there is used sodium hydroxide, potassium carbonate, sodium carbonate, sodium hydride, potassium t-butoxide, potassium hydroxide or the like. As the alkylating agent, there is used, for example, a halide (e.g. methyl iodide, ethyl iodide, propyl iodide, butyl iodide, and bromide or chloride thereof). The reaction is conducted usually at temperatures ranging from ice-cooling to the boiling point of the solvent used, while the reaction conditions vary with the base, the alkylating agent and the solvent employed.

The phenylenediamine (IV) is reacted with isothiocyanate to form the thiourea compound (V), which is then subjected to desulfurisation-cyclization to give the 2-substituted amino compound (Ij) as illustrated in Scheme I. The reaction is conducted by using about 1 to 3 mol. of isothiocyanate relative to 1 mol. of Compound (IV) usually in halogenated hydrocarbons (e.g. chloroform, methylene chloride, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.), aromatic hydrocarbons (e.g. benzene, toluene, etc.), alcohols (e.g. methanol, ethanol, etc.), acetonitrile, dimethylformamide or the like. The reaction can also be conducted without these solvents. Examples of such isothiocyanates include isothiocyanates of methyl, ethyl, propyl, isopropyl, butyl, etc. The reaction is conducted preferably at temperatures ranging from room temperatures to about 50°C for about 10 to 60 hours. The desulfurization-cyclization can be conducted in a manner as described below.

The reaction is conducted, in halogenated hdyrocarbons (e.g. $HgCl_2$), by using about 1 to 3 mol. of a metal halide (e.g. $HgCl_2$) relative to 1 mol. of the thiourea (V) obtained by the above-mentioned method. The reaction is conducted preferably at temperatures ranging from room temperature to the boiling point of a solvent employed for about 3 to 10 hours. The reaction can also be conducted by using about 1 to 3 mol.

of methyl iodide relative to 1 mol. of thiourea (V) in alcohols (e.g. methanol or ethanol), preferably at temperatures ranging from room temperature to about the boiling point of the solvent for about 3 to 15 hours.

The 2-halogeno compound (V') readily prepared from the compound (If) is reacted with various nucleophilic reagents to form the compound (I) as illustrated in Scheme I'. The reaction can be carried out according to the procedures as described in known references (e.g. D. Harrison and J. J. Ralph, J. Chem. Soc., 1965, 236). The compound (If) is reacted with a halogenating reagent (e.g. phosphorus oxychloride, phosphorus trichloride, etc.) to form the 2-halogeno compound (V') which is reacted with various nucleophilic reagents (e.g. alcohols, mercaptans, amines, etc.) in a suitable organic solvent to give the compound (I). The reaction conditions may vary depending on the nucleophilic reagent employed. Upon the reaction with alcohols, alcoholates (e.g. sodium methoxide, sodium ethoxide, sodium propoxide, etc.) derived from alcohols and sodium metal are preferably used. As the reaction solvent, alcohols then used for nucleophilic reagents can be employed. Relative to 1 mol. of the compound (V'), there is used about 2 to 5 mol. of an alcoholate. Advantageously, the reaction is usually conducted at approximately the boiling point of the solvent used for about 1 to 3 hours. Upon the reaction with amines, about 3 to 10 mol. of an amine is used relative to 1 mol. of the compound (V'). As the reaction solvent, alcohols (e.g. ethanol, etc.) are employed but, an excess amount of amines can be used. Advantageously, the reaction is usually conducted at temperatures ranging from about the boiling point of the solvent to 150°C for about 1 to 10 hours. Upon the reaction with mercaptans, about 2 to 5 mol. of a mercaptan is used relative to 1 mol. of the compound (V'). The reaction is preferably conducted in the presence of about 1 to 3 mol. of an base (e.g. sodium carbonate, potassium carbonate, etc.) relative to Compound (IV). Examples of solvents include acetonitrile, alcohols, halogenated hydrocarbons (e.g. chloroform, dichloroethane, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.) or amides (e.g. dimethylformamide, dimethylacetamide, etc.). The reaction can be conducted preferably at temperatures ranging from 50°C to about the boiling point of the solvent for about 1 to 5 hours.

The compound (Ih) is reacted with an oxidizing reagent (e.g. m-chloroperbenzoic acid, etc.) to form the sulfoxide or sulfone compound (Ih') which is reacted with various nucleophilic reagents (e.g. alcohols, amines, mercaptans, etc.) to give the compound (I) as illustrated in Scheme I''. The oxidation of the compound (Ih) to the sulfoxide or sulfone compound (Ih') is preferably conducted in solvents including halogenated hydrocarbons (e.g. dichloromethane, chloroform, dichloroethane, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.) and the like. Examples of such oxidising reagents include organic peracids such as m-chloroperbenzoic acid, N-halosuccinimides such as N-bromosuccinimide, etc. Generally, the oxidizing reagent is employed in an equal or slightly excess amount when compared to the compound (Ih). The sulfoxide can be produced by one mole of the oxidizing reagent and the sulfone compound (Ih') by two moles. The reaction is preferably conducted at temperatures ranging from about ice-cooled temperature to room temperature for about 3 to 10 hours.

The reaction of the compound (Ih') into the compound (I) is conducted in essentially the same manner as mentioned in Scheme I'.

The carboxylic acid (Ik) is formed by the alkaline hydrolysis of the carboxylic acid ester compound (Ij) as illustrated in Scheme J. The reaction is conducted by using about 1 to 3 mol. of alkali relative to 1 mol. of Compound (Ij) usually in a solvent such as an aqueous alcohol (e.g. methanol, ethanol, methyl cellosolve, etc.). Examples of such alkalis include sodium hydroxide, potassium hydroxide or the like. The reaction is conducted at temperatures ranging from room temperature to about 100°C for about 1 to 10 hours, preferably at about the boiling point of a solvent used for about 3 to 5 hours.

The protected tetrazole derivative (Il) is deprotected to give Compound (Im) as depicted in Scheme K. Conditions of the deprotection depend on the protective group (R) then used. When R is triphenylmethyl, 2-tetrahydropyranyl, methoxymethyl, ethoxy methyl or the like, it is convenient to conduct the reaction in an aqueous alcohol (e.g. methanol, ethanol, etc.) containing about 0.5N to 2N hydrochloric acid or acetic acid at about room temperatures for about 1 to 10 hours.

The compound (Iq) is prepared by protecting the tetrazole group in the presence of a base, and then the carboxyl group to give the ester compound (Ip), followed by removing the protective group under acid conditions as illustrated in Scheme L. In the reaction to obtain Compound (Io) from Compound (In), an alkylating agent is used in an amount of about 1 to 1.5 mol. relative to 1 mol. of Compound (In). Examples of the solvents to be used for the reaction include halogenated hydrocarbons such as chloroform, methylene chloride and ethylene chloride, ethers such as dioxane and tetrahydrofuran, acetonitrile, pyridine, etc. Examples of such bases include potassium carbonate, sodium carbonate, triethylamine, pyridine, etc. Examples of such alkylating agents include halides such as triphenylmethyl chloride and methoxy methyl chloride, etc. While reaction conditions vary with combinations of the base and the alkylating agent

employed, it is preferable to conduct the reaction by using triphenylmethyl chloride at temperatures ranging from ice-cooling to room temperature for about 1 to 3 hours in methylene chloride in the presence of triethylamine. In the reaction for producing Compound (Ip) from Compound (Io) thus obtained, the alkylating agent is used in an amount of about 1 to 3 mol. relative to 1 mol. of Compound (Iq). Examples of the reaction solvent include amides such as dimethylformamide and dimethylacetamide, acetonitrile, dimethylsulfoxide, acetone, ethyl methyl ketone, etc. Examples of the base include potassium carbonate, sodium carbonate, sodium hydride, potassium t-butoxide, etc. Examples of such alkylating agents include halides such as cyclohexyl 1-iodoethyl carbonate, ethyl 1-iodoethyl carbonate, pivaloyloxymethyl iodide, etc. While reaction conditions vary with combinations of the base and the alkylating agent employed, it is preferable to subject Compound (Io) to reaction in DMF, by adding the alkylating agent in the presence of potassium carbonate, at about room temperatures for about 30 minutes to one hour.

The reaction for deprotecting Compound (Ip) thus obtained is conducted preferably in a manner similar to the reaction (K). When trityl group is used as the protecting group of tetrazole group, it is preferable to conduct the reaction in methanol or ethanol, while adding 1N-HCl, at about room temperatures for about 30 minutes to one hour.

The reaction products obtained as above by the reaction processes (A) to (L), can be easily isolated and/or purified by or according to conventional methods such as, for example, evaporation of solvents, extraction by water or organic solvents, concentration, neutralization, recrystallization, distillation, column chromatography and the like. The compounds (I) thus produced via the reaction processes as depicted in Schemes A to L can be isolated and/or purified from the reaction mixture according to conventional methods such as, for example, recrystallization and column chromatography, to obtain a crystalline product.

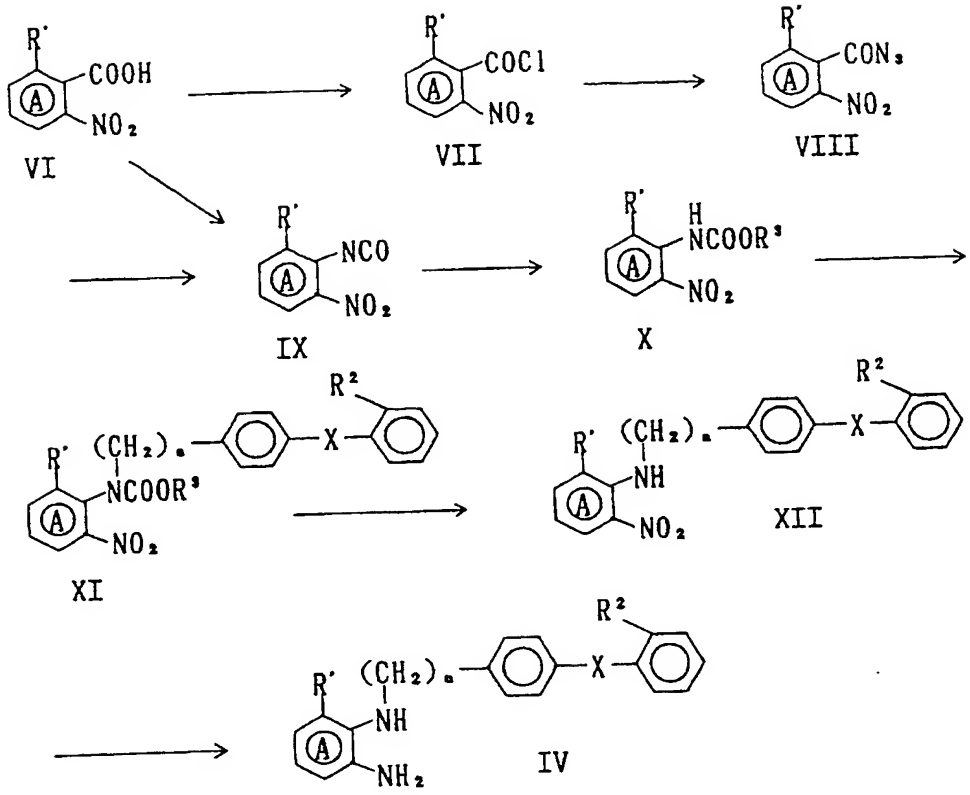
The compounds obtained as above by the reaction processes (A) to (L), may be in the form of solvates or salts (including addition salts) derived from pharmaceutically or physiologically acceptable acids or bases. These salts include but are not limited to the following: salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, citric acid, ascorbic acid, lactic acid, p-toluenesulfonic acid, methanesulfonic acid, fumaric acid, tartaric acid and maleic acid. Other salts include salts with ammonium, alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases (e.g. trialkylamines, dibenzylamine, ethanolamine, triethanolamine, N-methylmorpholine, etc).

And, by conventional means, the compounds (I) can be formed as salts with non-toxic, physiologically or pharmaceutically acceptable acids or bases, for example salts with an inorganic acid such as hydrochloride, sulfate or nitrate, and, depending on compounds, salts with an organic acid such as acetate, oxalate, succinate or maleate, salts with an alkali metal such as sodium salt or potassium salt, or salts with an alkaline earth metal such as calcium salt.

For the synthesis of these compounds (I), the starting compounds (II) and (IV) can be synthesized by or according to the methods described in, for example, the following literature references or methods analogous thereto, namely, by the reactions (M), (N), (O) and (P) as depicted below.

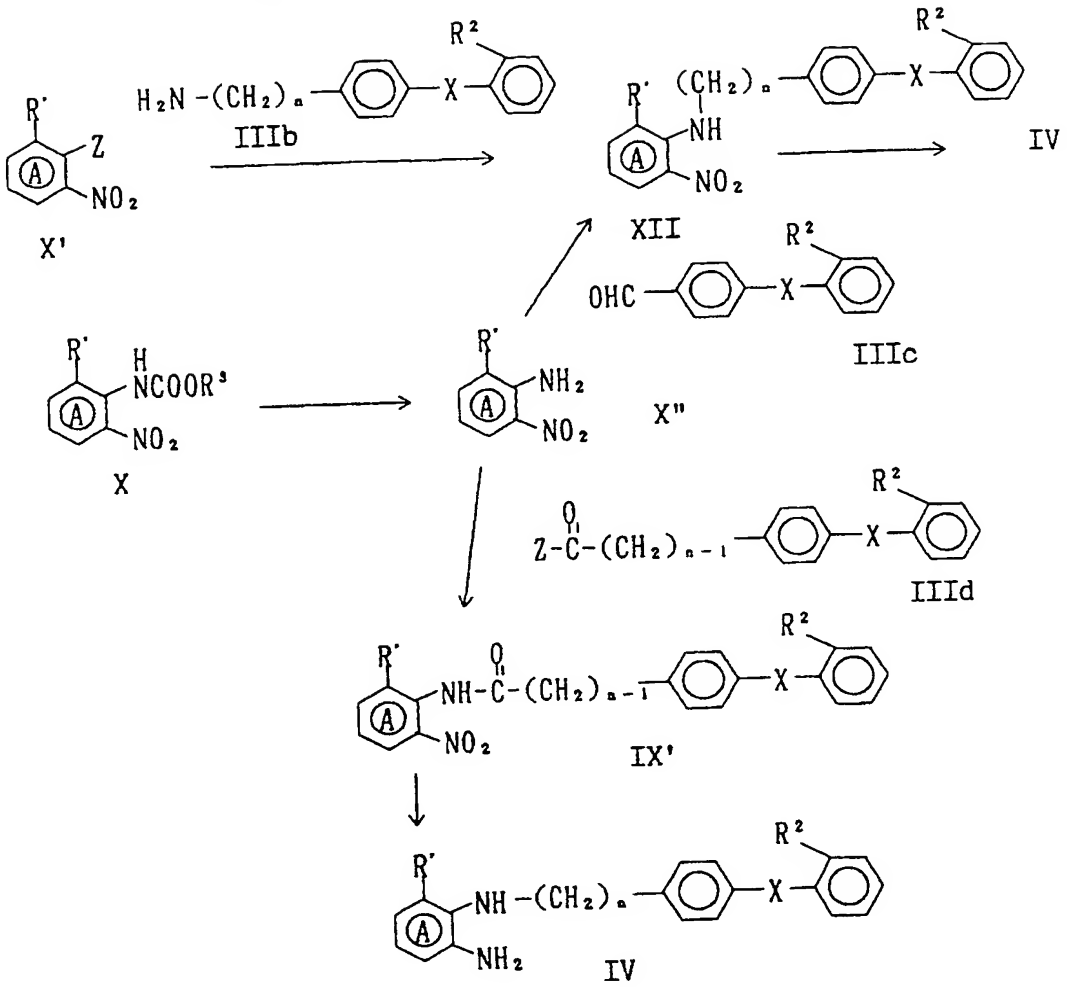
(1) P. N. Preston, The Chemistry of Heterocyclic Compounds, Vol. 40, ed. by P. N. Preston, John Wiley & Sons Inc., New York (1981), pp. 1-286,
(2) E. S. Schipper and A. R. Day, Heterocyclic Compounds, Vol. 5, ed. by R. C. Elderfield, John Wiley & Sons Inc., New York (1965), pp. 194-297,
(3) N. J. Leonard, D. Y. Curtin, & K. M. Beck, J. Am. Chem. Soc. 69, 2459 (1947),
(4) S. Weiss, H. Michaud, H. Prietzel, & H. Kromer, Angew. Chem. 85, 866 (1973),
(5) W. B. Wright, J. Heterocycl. Chem., 2, 41 (1965),
(6) A. M. E. Omar, Synthesis, 1974, 41,
(7) D. J. Brown & R. K. Lynn, J. Chem. Soc.(Perkin I), 1974, 349,
(8) J. A. Van Allan & B. D. Deacon, Org. Syn., 30, 56 (1950),
(9) S. P. Singh, S. S. Parmar & B. R. Pandey, J. Heterocycl. Chem., 14, 1093 (1977),
(10) S. Nakajima, I. Tanaka, T. Seki & T. Anmo, Yakugaku Zasshi, 78, 1378 (1959),
(11) K. Seno, S. Hagishita, T. Sato & K. Kuriyama, J. Chem. Soc., Perkin Trans. 1984, 2013,
(12) D. R. Buckle et al., J. Med. Chem., 30, 2216 (1987),
(13) R. P. Gupta, C. A. Larroquette & K. C. Agrawal, J. Med. Chem., 25, 1342 (1982), etc.

Scheme M



[wherein R^2, R', A, X and n are of the same meaning as defined above; and R^3 stands for a lower (C_{1-4}) alkyl group].

Scheme M'



wherein R^2, R^3, R', A, Z, X and n are of the same meaning as defined above.

Schemes M and M' illustrate the process for preparing important intermediates which are useful in synthesizing the compound (I) of the present invention.

These compounds can be produced according to the above-mentioned references. The compound (VI) is converted by the Curtius reaction into the carbamic acid compound (X) followed by alkylation and subsequent reduction of nitro to form the diamino compound (IV). In the rearrangement of Compound (VI) to Compound (X), Compound (X) is produced in a high yield according to conventional procedures of the Curtius rearrangement: the acid chloride (VII) → the acid azide (VIII) → the isocyanate (IX) → Compound (X). The compound (VI) is conveniently heated with diphenylphosphoryl azide (DPPA) in the presence of triethylamine in DMF to form the isocyanate (IX) via the acid azide (VIII) followed by reaction of an alcohol to give the compound (X) in a high yield. The compound (X) thus obtained is alkylated in the same manner as in Scheme A to form the compound (XI). In the reaction, it is convenient to heat the reaction mixture under reflux for about 4 - 6 hours in the presence of potassium carbonate as a base in acetonitrile. The compound (XI) is heated under reflux in an alcohol containing a mineral acid (e.g. hydrochloric acid, sulphuric acid, etc.) or an organic acid (e.g. trifluoroacetic acid, etc.), for about 1 - 2 hours to give the compound (XII). Various reducing reagents (e.g. raney nickel, stannic chloride, etc.) can be employed in the reduction of the nitro compound (XII) to the diamino compound (IV). Among them, the combination of ferric chloride and hydrazine • hydrate in an alcohol is the most convenient. Further, the compound (IV) can be prepared by various techniques other than those mentioned above.

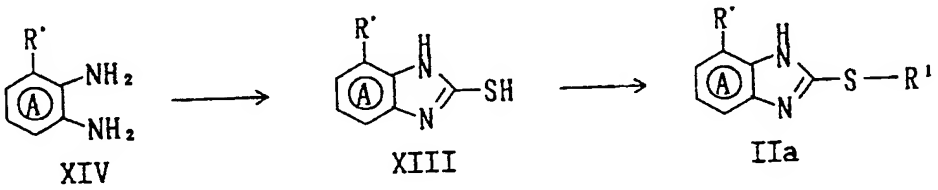
The compound (X') commercially available or readily obtained by known methods in the art is preferably reacted with the amine (IIIb) in the presence of a base (e.g. potassium carbonate, sodium carbonate, amines, etc.) in an organic solvent (e.g. alcohols, ethers, halogenated hydrocarbons, amides,

etc.) at temperatures ranging from about the boiling point of the solvent to 100°C for about 5 to 20 hours.

The compound (X'') readily obtained by acid treatment of the compound (X) is subjected to condensation under dehydration conditions including azeotropic removal of water (or in the presence of a dehydrating agents) in an organic solvent (e.g. ethers, halogenated hydrocarbons, aromatic hydrocarbons, etc.) followed by reaction with a reducing reagent (e.g. $NaCNBH_3$, etc.) to form the compound (XII). The condensation under dehydration conditions can be accelerated by using conventional acid or base catalysts.

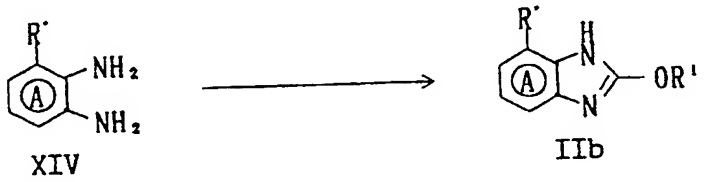
The compound (X'') is reacted with the acid chloride (IIId), preferably in the presence of a base (e.g. pyridine, triethylamine, dimethylaminopyridine, etc.) in an organic solvent (e.g. halogenated hydrocarbons, pyridine, etc.) at temperatures ranging from room temperature to about the boiling point of the solvent for about 2 to 20 hours, to the amide (XI'). The resulting amide (XI') is reacted with a reducing reagent (e.g. sodium aluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, etc.) to form the diamino (IV).

Scheme N



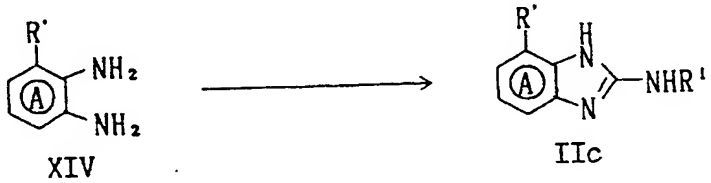
[wherein each group is of the same meaning as defined above].

Scheme O



[wherein each group is of the same meaning as defined above].

Scheme P

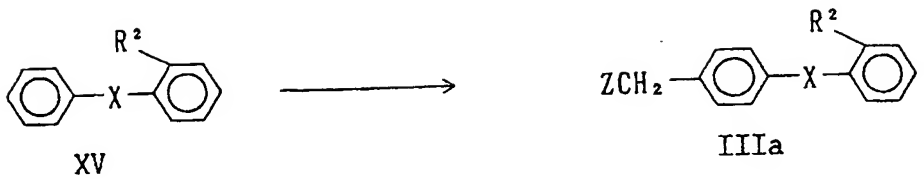


[wherein each group is of the same meaning as defined above].

And, among the starting compounds (III), the compound (III) wherein n denotes 1, i.e. the compound (IIIa) is commercially available, or can be readily obtained also by subjecting Compound (XV) to halogenomethylation in accordance with the methods described in literature references, for example;

1) J. R. E. Hoover, A. W. Chow, R. J. Stedman, N. M. Hall, H. S. Greenberg, M. M. Dolan and R. J. Feriauto, J. Med. Chem., 7, 245 (1964),
2) R. J. Stedman, J. R. E. Hoover, A. W. Chow, M. M. Dolan, N. M. Hall and R. J. Feriauto, J. Med. Chem., 7, 251 (1964),
3) H. Gilman and R. D. Gorsich, J. Am. Chem. Soc., 78, 2217 (1956),
4) M. Orchin and E. Oscar Woolfolk, J. Am. Chem. Soc., 67, 122 (1945), etc.

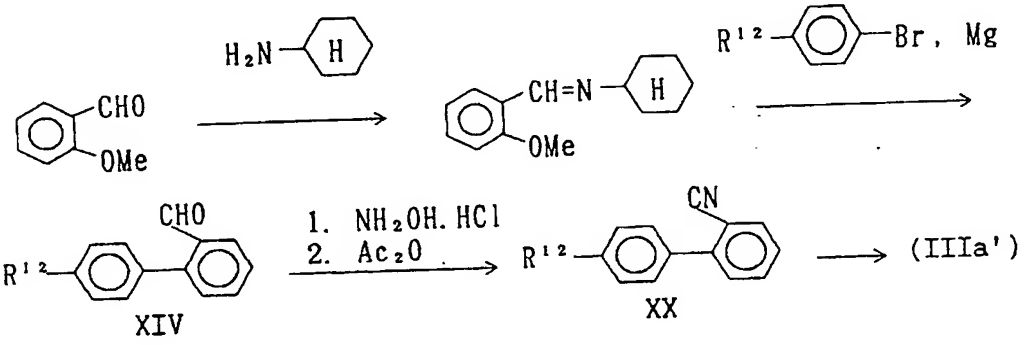
Scheme Q



[wherein each group is of the same meaning as defined above].

The compound (IIIa') can also be readily prepared according to the methods described in L. N. Pridgen, L. Snyoler and J. Prol, Jr., J. Org. Chem., 54, 1523 (1989) as illustrated in Scheme R, followed by halogenation (R^{12} = Me) or halogenomethylation (R^{12} = H).

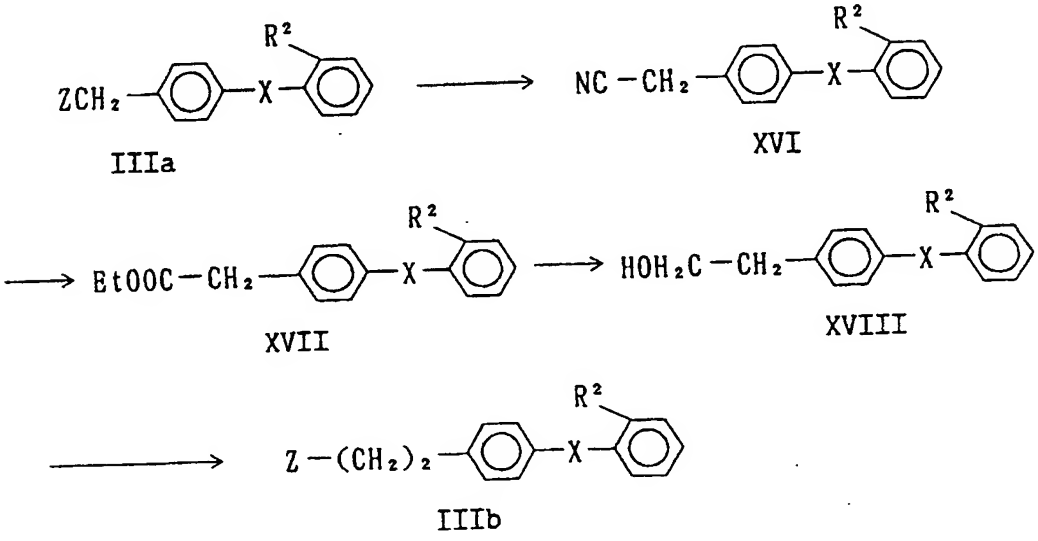
Scheme R



[wherein R^{12} is hydrogen or methyl].

Further, among the starting compounds (III), the compound (III) wherein n denotes 2, i.e. the compound (IIIb) can be obtained from the compound (IIIa) in accordance with the reaction (S).

Scheme S



[wherein each group is of the same meaning as defined above].

The compounds and the salts thereof thus produced are less toxic, strongly inhibit the vasoconstrictive and hypertensive actions of angiotensin II, exert a hypotensive effect in animals, in particular mammals (e.g. human, dog, rabbit, rat, etc.), and therefore they are useful as therapeutics for not only hypertension but also circulatory diseases such as heart failure (hypertrophy of the heart, cardiac insufficiency, cardiac infarction or the like), strokes, cerebral apoplexy, nephropathy and nephritis. The compounds (I) and salts thereof according to the present invention strongly inhibit vasoconstriction and hypertension derived by angiotensin II and therefore possess potent anti-hypertensive activity in animals, more specifically mammal animals (e.g. humans, dogs, pigs, rabbits, rats, etc.). Further, the compounds (I) and salts thereof according to the present invention are of quite low toxicity and clinically useful in treating not only hypertension but also circulatory system diseases such as heart and brain diseases, strokes, renal failures, nephritis and the like.

For therapeutic use, the compounds (I) and salts thereof can be orally, parenterally, by inhalation spray, rectally, or topically administered as pharmaceutical compositions or formulations (e.g. powders, granules, tablets, pills, capsules, injections, syrups, emulsions, elixirs, suspensions, solutions and the like) comprising at least one such compound alone or in admixture with pharmaceutically acceptable carriers, adjuvants, vehicles, excipients and/or diluents. The pharmaceutical compositions can be formulated in accordance with conventional methods. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intraperitoneal injections, or infusion techniques. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in water. Among the acceptable vehicles or solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil or fatty acid may be employed including natural, synthetic, or semi-synthetic fatty oils or acids, and natural, synthetic, or semi-synthetic mono-, di-, or triglycerides.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug. Solid dosage forms for oral administration may include powders, granules, tablets, pills, and capsules as mentioned above. In such solid dosage forms, the active compound may be admixed with at least one additive such as sucrose, lactose, celluloses, mannitol, maltitol, dextran, starches, agars, alginates, chitins, chitosans, pectins, tragacanth gums, arabic gums, gelatins, collagens, casein, albumin, and synthetic or semi-synthetic polymers or glycerides. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents as magnesium stearate, preservatives such as parabens and sorbic acid, antioxidants such as ascorbic acid, α-tocopherol and cysteine, disintegrants, binders, thickening, buffering, sweetening, flavoring, and perfuming agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, solutions containing inert diluents commonly used in the art, such as water.

Specific dose levels for any particular patient will be employed depending upon a variety of factors including the activity of specific compounds employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The dose varies with the diseases to be treated, symptoms, subjects and administration routes, and it is desirable that a daily dose of 1 to 50 mg for oral administration or 1 to 30 mg for intravenous injection is divided into 2 to 3 administrations when used as an agent for the therapy in adults. For example, when used for treating adult essential hypertension, the active ingredient will preferably be administered in an appropriate amount, for example, about 10 mg to 100 mg a day orally and about 5 mg to 50 mg a day intravenously. The active ingredient will preferably be administered in equal doses two or three times a day.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds.

Examples

By the following formulation examples, working examples, experimental examples and reference

examples, the present invention will be explained more concretely, but they should not be interpreted as limiting the invention in any manner.

Examples of abbreviations in this specification are as follows:

Me: methyl, Et: ethyl, Tet: tetrazolyl, cycl: cyclo-, Pr: propyl, Bu: butyl, Pen: pentyl, Bu: butyl, Hex: hexyl, Hep: heptyl, Ph: phenyl, DMF: dimethylformamide, and THF: tetrahydrofuran.

Formulation Examples

When the compound (I) of the present invention is used as a therapeutic agent for circulatory failures such as hypertension, heart diseases, strokes, kidney diseases, etc., it can be used in accordance with, for example, the following formulations.

1. Capsules

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]benzimidazole-7-carboxylic acid	10 mg
(2)	lactose	90 mg
(3)	fine crystalline cellulose	70 mg
(4)	magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

2. Tablets

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]benzimidazole-7-carboxylic acid	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	fine crystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
	one tablet	230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

3. Injections

(1)	2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid disodium salt		10 mg
(2)	inositol		100 mg
(3)	benzyl alcohol		20 mg
		one ampoule	130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.

4. Capsules

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate		10 mg
(2)	lactose		90 mg
(3)	fine crystalline cellulose		70 mg
(4)	magnesium stearate		10 mg
		one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

5. Tablets

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate		10 mg
(2)	lactose		35 mg
(3)	corn starch		150 mg
(4)	fine crystalline cellulose		30 mg
(5)	magnesium stearate		5 mg
		one tablet	230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

6. Injections

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]benzimidazole-7-carboxylic acid disodium salt		10 mg
(2)	inositol		100 mg
(3)	benzyl alcohol		20 mg
		one ampoule	130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.

Reference Example 1

2-Propoxybenzimidazole

To a solution of o-phenylenediamine (2 g) in propyl orthocarbonate (5 ml) was added acetic acid (1.1 ml) and the solution was stirred at 80° C for 3 hours. To the reaction mixture was added ethyl acetate, and the solution was washed with an aqueous solution of sodium hydrogen carbonate and water, then dried (Na_2SO_4), followed by concentration to dryness. The concentrate was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (1.54 g, 47%), m.p. 163-164° C.

Reference Example 2

Ethyl 2-carboxy-3-nitrobenzoate

A mixture of 3-nitrophthalic acid (35 g) in ethanol (300 ml) containing conc. sulfuric acid (20 ml) was heated under reflux for 24 hours. The solvent was evaporated in vacuo and the residue was poured into cold water (700 ml). The mixture was extracted with ethyl acetate. The organic layer was washed with water and shaken with an aqueous solution of potassium carbonate.
The aqueous layer was made acidic with hydrochloric acid and the mixture was extracted with methylene chloride. The organic layer was washed with water, then dried, followed by evaporation of the solvent. The resultant solid (29 g, 74%) was used for the subsequent reaction without purification.
^{1}H-NMR(90MHz, $CDCl_3$) δ : 1 .43(3H,t), 4.47(2H,q), 7.70(1H,t), 8.40(2H,d), 9.87(1H,br s)
IR(Nujol) cm^{-1}: 1725, 1535, 1350, 1300, 1270

Reference Example 3

Ethyl 2-t-butoxycarbonylamino-3-nitrobenzoate

A mixture of ethyl 2-carboxy-3-nitrobenzoate (23.9 g) and thionyl chloride (12 ml) in benzene (150 ml) were heated under reflux for 3 hours. The reaction mixture was concentrated to dryness. The resultant acid chloride (26 g, quantitative) was dissolved in methylene chloride (20 ml). The solution was added dropwise to a mixture of sodium azide (9.75 g) in dimethylformamide(DMF) (20 ml) with stirring vigorously. The reaction mixture was poured into a mixture of ether-hexane (3 : 1, 200 ml) and water (250 ml) to separate into two layers. The organic layer was washed with water, then dried, followed by evaporation of the solvent. The residue was dissolved in t-butanol (200 ml) and the solution was heated gradually with stirring, followed by heating under reflux for 2 hours. The reaction mixture was concentrated in vacuo to give an oily product (30 g).
^{1}H-NMR(90MHz, $CDCl_3$) δ : 1.40(3H,t), 1.53(9H,s), 4.43(2H,q), 7.23(1H,t), 8.03-8.27(2H,m), 9.70(1H,br s)
IR(Neat) cm^{-1}: 3320, 2980, 1740, 1585, 1535, 1500, 1440, 1375, 1265, 1155

Working Example 1

Ethyl 2-[[2'-cyanobiphenyl)]amino]-3-nitrobenzoate

To a solution of ethyl 2-t-butoxycarbonylamino-3-nitrobenzoate (20 g) in tetrahydrofuran (50 ml) was added, while stirring under ice-cooling, sodium hydride (60% dispersion in mineral oil, 2.8 g). The mixture was stirred at room temperature for 20 minutes and to the mixture were then added 4-(2-cyanophenyl)-benzyl bromide (18 g) and potassium iodide (360 mg), followed by heating for 10 hours under reflux. The solvent was evaporated to dryness and the residue was partitioned between water (250 ml) and ether (200 ml). The organic layer was washed with water, dried and concentrated to give a yellow syrup. The syrup was dissolved in a mixture of trifluoroacetic acid (60 ml) and methylene chloride (40 ml) and the solution was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and to the residue was added ethyl ether (200 ml) to give crystals. The crystals were collected by filtration, washed with ether to give pale yellow crystals (22.1 g, 85%), m.p. 118-119° C.
^{1}H-NMR(90MHz,$CDCl_3$) δ : 1.37(3H,t), 4.23(2H,s), 4.37(2H,q), 6.37(1H,t), 7.33-7.83(9H,m), 7.97-8.20(2H,m)
IR(Nujol)cm-1: 3280, 2220, 1690, 1575, 1530, 1480, 1450, 1255, 1105, 755

Working Example 2

Ethyl 3-amino-2-[[2'-cyanobiphenyl-4-yl)methyl]amino]benzoate

To a solution of ethyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]nitrobenzoate (10.4 g) in ethanol (50 ml) was added stannous dichloride dihydrate (28.1 g) and the mixture was stirred at 80° C for two hours. The solvent was evaporated to dryness. To the ice-cooling mixture of the residue in ethyl acetate (300 ml) was added dropwise 2N NaOH (500 ml) with stirring. The aqueous layer was extracted with ethyl acetate (200 ml x 2). The organic layers were combined, washed with water, and dried. The solvent was evaporated to dryness and the residue was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - hexane gave colorless crystals (7.3 g, 79%), m.p. 104-105° C.
^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.33(3H,t), 4.23(2H,s), 4.27(2H,q), 6.83-6.93(2H,m), 7.35-7.55(7H,m), 7.64-(1H,dt), 7.76(dd)
IR(KBr) cm^{-1}: 3445, 3350, 2220, 1680, 1470, 1280, 1240, 1185, 1160, 1070, 1050, 1020, 805, 750

Working Example 3

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxybenzimidazole-7-carboxylate

Acetic acid (0.2 g) was added to a solution of ethyl 3-amino-2-[[2'-cyanobiphenyl-4-yl)methyl]amino]-benzoate (1.1 g) in methyl orthocarbonate (5 ml). The mixture was stirred at 80° C for one hour. The reaction mixture was concentrated, and the concentrate was extracted with ethyl acetate. The organic layer was then washed with an aqueous solution of sodium hydrogen carbonate and water. The solvent was evaporated in vacuo to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (1.09 g, 90%), m.p. 160-161° C.
^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.23(3H,t), 4.23(2H,q), 4.26(3H,s), 5.72(2H,s), 7.09(2H,d), 7.20(1H,t), 7.38-7.48-(4H,m), 7.58-7.66(2H,m), 7.73-7.79(2H,m)
IR(KBr) cm^{-1}: 3000, 2220, 1725, 1560, 1465, 1440, 1415, 1285, 1250, 1220, 1040, 760, 750, 740

Working Example 4

Ethyl 1-[(2'cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate

Acetic acid (0.2 g) was added to a solution of ethyl 3-amino-2-N-[2'-cyanobiphenyl-4-yl)methyl]-aminobenzoate (1.0 g) in ethyl orthocarbonate (5 ml). The mixture was stirred at 80° C for one hour. The reaction mixture was concentrated, and the concentrate was dissolved in ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate and water. The solvent was evaporated to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (0.79 g, 69%), m.p. 131-132° C.

Elemental Analysis for $C_{26}H_{23}N_3O_3$:

	C(%)	H(%)	N(%)
Calcd.:	73.39;	5.45;	9.88
Found :	73.36;	5.42	9.83

^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.24(3H,t), 1.49(3H,t), 4.24(2H,q), 4.68(2H,q), 5.72(2H,s), 7.10(2H,d), 7.19(1H,t), 7.38-7.46(4H,m), 7.56-7.66(2H,m), 7.73-7.77(2H,m)
IR(KBr) cm^{-1}: 2220, 1720, 1550, 1480, 1430, 1280, 1245, 1215, 1040, 760, 740

Working Example 5

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-propoxybenzimidazole-7-carboxylate

Acetic acid (0.2 g) was added to a solution of ethyl 3-amino-2-N-[[(2'-cyanobiphenyl-4-yl)methyl]amino]-benzoate (0.9 g) in propyl orthocarbonate (5 ml). The mixture was stirred at 80° C for one hour. The reaction mixture was concentrated, and the concentrate was dissolved in ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate. The solvent was evaporated to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (0.72 g, 68%), m.p. 90-92° C.

Elemental Analysis for $C_{27}H_{25}N_3O_3$:

	C(%)	H(%)	N(%)
Calcd.:	73.79;	5.73;	9.56
Found :	73.84;	5.79;	9.54

^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.01 (3H,t), 1.25(3H,t), 1.80-1.97(2H,m), 4.24(2H,q), 4.57(2H,q), 5.72(2H,s), 7.11(2H,d), 7.19(1H,t), 7.38-7.46(4H,m), 7.56-7.66(2H,m), 7.73-7.77(2H,m)
IR(KBr) cm^{-1}: 2220, 1725, 1550, 1480, 1460, 1430, 1370, 1280, 1245, 1210, 1115, 1040, 760, 750, 740

Working Example 6

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-mercaptobenzimidazole-7-carboxylate

A mixture of ethyl 3-amino-2-N-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate (5.6 g) and sodium O-ethyl dithiocarbonate (7.3 g) in ethanol (50 ml) was heated for 8 hours under reflux. The reaction mixture was concentrated and the residue was dissolved in water. The solution was adjusted to pH 3-4 with hydrochloric acid. Precipitating crystals were collected by filtration, followed by recrystallization from ethanol to afford yellow crystals (5.0 g, 80%), m.p. 225-227° C.
^{1}H-NMR(200MHz, DMSO-d_6) δ : 1.08(3H,t), 4.12(2H,q), 5.90(2H,brs), 7.08(2H,d), 7.27(1H,t), 7.38-7.59(6H,m), 7.76(1H,dt), 7.92(1H,dd)
IR(KBr) cm^{-1}: 2210, 1720, 1460, 1440, 1420, 1375, 1335, 1265, 1180, 1135, 1115, 1100, 985, 760, 740

Reference Example 4

Methyl 2-[[(2'-cyanobiphenyl)methyl]amino]-3-nitrobenzoate

A mixture of ethyl 2-[[(2'cyanobiphenyl)methyl]amino]-3-nitrobenzoate (5 g) and sodium hydride (60% dispersion in mineral oil, 1.62 g) in methanol (50 ml) was stirred at room temperature for one day. The reaction mixture was concentrated and the residue was poured into a saturated aqueous solution of sodium hydrogen carbonate (100 ml), followed by extraction with chloroform. The organic layer was washed with water, dried and concentrated to dryness to give crystals. Recrystallization from ethyl acetate - hexane afforded pale yellow crystals (3.98 g, 83%), m.p. 106-108° C.

^{1}H-NMR(200MHz, $CDCl_3$) δ : 3.81(3H,s), 3.97(2H,br s), 4.23(2H,s), 6.40(1H,br s), 6.88-6.91(2H,m), 7.34-7.55-(7H,m), 7.65(1H,dt,J = 1.2, 7.7Hz), 7.77(1H,dd,J = 1.4,8.OHz)
IR(KBr) cm^{-1}: 3410, 3350, 2225, 1695, 1485, 1470, 1290, 1200, 780, 760

Working Example 7

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate

Acetic acid (0.37 g) was added to a solution of methyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]-amino]benzoate (2.03 g) in ethyl orthocarbonate (5 ml), and the mixture was stirred at 80° C for one hour. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate and water. The solvent was evaporated in vacuo to give crystals. Recrystallization from ethyl acetate - hexane afforded colorless crystals (2.01 g, 86%), m.p. 168.5-169.5° C.

Elemental Analysis :

	C(%)	H(%)	N(%)
Calcd.:	72.98;	5.14;	10.21
Found :	72.71;	5.12;	9.97

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.42(3H,t,J = 7.1Hz), 3.71(3H,s), 4.63(2H,q,J = 7.1Hz), 5.59(2H,s), 7.09-(2H,d,J = 8.4Hz), 7.20(1H,t,J = 7.9Hz), 7.45-7.59(5H,m), 7.69-7.80(2H,m), 7.92(1H,dd,J = 1.4,7.8Hz)
IR(KBr) cm^{-1}: 2225, 1725, 1550, 1480, 1430, 1350, 1280, 1250, 1040, 760, 750

Reference Example 5

Ethyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-(3-ethylthioureido)benzoate

A mixture of ethyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate (1.61 g), ethyl isothiocyanate (1.5 ml) and ethanol (1 ml) was stirred at room temperature for 3 days. The reaction mixture was dissolved in ethyl acetate and the solution was washed with water, dried and concentrated to dryness to give crystals. Recrystallization from ethyl acetate - hexane afforded pale yellow crystals (1.92 g, 91%), m.p. 108-110° C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.15(3H,t), 1.40(3H,t), 3.50-3.70(2H,brs), 4.37(2H,q), 4.56(2H,d), 6.07(1H,t), 6.78-(1H,t), 7.19-7.24(1H,m), 7.38-7.53(6H,m), 7.63(1H,dt), 7.72-7.76(1H,m), 7.99(1H,dd), 8.29(1H,br s)
IR(KBr) cm^{-1}: 3375, 3320, 3150, 2975, 2220, 1740, 1680, 1540, 1510, 1450, 1300, 1225, 1180, 1150, 760, 750

Reference Example 6

Ethyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-(3-propylthioureido)benzoate

In substantially the same manner as Reference Example 5, desired pale yellow syrup (2.0 g, 98%) was obtained from ethyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate (1.6 g), propyl isothiocyanate (1.5 ml) and ethanol (1 ml).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.88(3H,t), 1.40(3H,t), 1.48-1.67(2H,m), 3.42-3.68(2H,br s), 4.37(2H,q), 4.56-(2H,d), 6.13(1H,t), 6.78(1H,t), 7.21-7.25(1H,m), 7.36-7.53(6H,m), 7.64(1H,dt), 7.73-7.77(1H,m), 7.99(1H,dd), 8.20-8.40(1H,br s)
IR(Neat)cm^{-1}: 3325, 3175, 2960, 2930, 2875, 2220, 1710, 1690, 1590, 1475, 1360, 1175, 1140, 1090, 1020, 760

Working Example 8

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethylaminobenzimidazole-7-carboxylate

Methyl iodide (4.5 g) was added to a solution of ethyl 2-[[(2'-cyanobiphenyl-4-yl) methyl]amino]-3-(ethylthioureido)benzoate (1.8 g) in ethanol (50 ml), and the mixture was heated under reflux for 12 hours. To the reaction mixture was added 1N-HCl (60 ml) and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness and the concentrate was dissolved in ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate and water and dried. The solvent was evaporated to dryness and the residue was purified by column chromatography on silica gel to afford yellow syrup (0.96 g, 58%).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.23(6H,t), 3.48-3.62(2H,m), 4.09(1H,t), 4.23(2H,q), 5.57(2H,s), 7.15(1H,t), 7.25-(2H,d), 7.40-7.77(8H,m)
IR(Neat)cm^{-1}: 3400, 3225, 2975, 2930, 2210, 1710, 1610, 1570, 1480, 1425, 1365, 1320, 1270, 1250, 1210, 1130, 1100, 1060, 770, 750

Working Example 9

Ethyl 1[(2'-cyanobiphenyl-4-yl)methyl]-2-propylaminobenzimidazole-7-carboxylate

In substantially the same manner as Working Example 8, desired yellow syrup (1.2 g, 65%) was obtained from a solution of ethyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-(3-propylthioureido)benzoate (2.0 g) and methyl iodide (4.8 g) in ethanol (50 ml).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.87(3H,t), 1.25(6H,t), 1.52-1.70(2H,m), 3.42-3.52(2H,m), 4.12(1H,t), 4.25(2H,q), 5.58(2H,s), 7.16(1H,t), 7.29(2H,d), 7.41-7.78(8H,m)
IR(Neat)cm^{-1}: 3400, 3250, 2975, 2950, 2890, 2225, 1715, 1620, 1590, 1570, 1480, 1430, 1370, 1285, 1220, 1135, 1070, 760

Working Example 10

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxybenzimidazole-7-carboxylate

A solution of 5.2M sodium methoxide in methanol (0.5 ml) was added to a solution of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxybenzimidazole-7-carboxylate (1.3 g) in methanol (50 ml). The mixture was heated for 4 hours under reflux. The reaction mixture was concentrated, and the precipitated crystals were collected by filtration. Recrystallisation from methanol afforded colorless prisms (1.1 g, 85%), m.p. 149-150 °C.

Elemental Analysis for $C_{24}H_{19}N_3O_3$:

	C(%)	H(%)	N(%)
Calcd.:	72.53;	4.82;	10.57
Found :	72.38;	4.93;	10.44

^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.75(3H,s), 4.26(3H,s), 5.69(2H,s), 7.09(2H,d), 7.23(1H,t), 7.37-7.46(3H,m), 7.55-7.65(2H,m), 7.72-7.78(2H,m)

Reference Example 7

Methyl 2-[[(2'-cyanobiphenyl-4-yl)]methyl]amino-3-(3-methylthioureido) benzoate

The above compound was synthesized (86 % yield) in substantially the same manner as Reference Example 5. m.p. 152-155 °C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.05-3.07(3H,br s), 3.92(3H,s), 4.58(2H,d), 6.04-6.08(1H,br s), 6.77(1H,t), 7.22-7.26(1H,m), 7.39-7.52(6H,m), 7.63(1H,dt), 7.75(1H,dd), 7.97(1H,dd), 8.28(1H,br s)
IR(KBr) cm^{-1}: 3375, 3325, 3175, 2220, 1680, 1590, 1540, 1500, 1480, 1450, 1435, 1265, 1230, 1190, 1145, 1050, 830, 760, 740

Working Example 11

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylaminobenzimidazole-7-carboxylate

The above compound was synthesized as a syrup (42% yield) in substantially the same manner as Working Example 8.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.11 (3H,d), 3.73(3H,s), 4.22(1H,q), 5.54(2H,s), 7.17(1H,t), 7.27(2H,d), 7.41-7.79-(8H,m)
IR(Neat)cm^{-1}: 3400, 3250, 3025, 2950, 2220, 1720, 1625, 1610, 1580, 1480, 1410, 1340, 1280, 1240, 1210, 1130, 1060, 750

Reference Example 8

2-Propoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole

Sodium hydride (60% dispersion in mineral oil, 0.24 g) was added to a stirred solution of 2-propoxybenzimidazole (0.71 g) in DMF (10 ml) under ice-cooling. The mixture was stirred for 20 minutes, to which was added N-triphenylmethyl-5-[2-(4-bromomethylbiphenyl]tetrazole (2.3 g), followed by stirring at room temperature for 5 hours. To the reaction mixture was added ice-water, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated to dryness. The concentrate was dissolved in methanol (50 ml), to which was added 1N-HCl (15 ml), followed by stirring at 60° C for 2 hours. The reaction mixture was concentrated, to which were added water (15 ml) and ethyl acetate (15 ml). The mixture was made alkaline with 1N NaOH and shaken. The aqueous layer was adjusted to pH 3-4 with 1N-HCl and then extracted with chloroform. The organic layer was washed with water, dried and concentrated to dryness. The concentrate was purified by column chromatography on silica gel to yield crystals. Recrystallization from ethyl acetate - methanol gave colorless crystals (0.58 g, 35%), m.p. 177-179° C (decomp.).

Elemental Analysis for $C_{24}H_{22}N_6O$:

	C(%)	H(%)	N(%)
Calcd.:	70.23;	5.40;	20.47
Found:	69.93;	5.43;	20.22

^{1}H-NMR(200MHz,DMSO-d_6) δ : 0.95(3H,t), 1.70-1.88(2H,m), 4.46(2H,t), 5.23(2H,s), 7.04-7.10(4H,m), 7.20-(2H,d), 7.38-7.43(2H,m), 7.48-7.70(4H,m)
IR(KBr) cm^{-1}: 1540, 1535, 1485, 1475, 1450, 1425, 1385, 1285, 1270, 1040, 980, 755, 745

Working Example 12

Methyl 2-butylamino-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

The title compound was prepared from methyl [[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-(butylureido)-benzoate in substantially the same manner as Working Example 8. The yield was quantitative.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.89(3H,t), 1.21-1.39(2H,m), 1.45-1.60(2H,m), 3.50-3.65(3H,brs), 3.92(3H,s), 4.56(2H,d), 6.08(1H,t), 6.78(1H,t), 7.21-7.30(1H,m), 7.39-7.54(6H,m), 7.64(1H,dt), 7.75(1H,dd), 7.98(1H,dd), 8.26(1H,brs)

Working Example 13

Methyl 2-(N-ethylmethylamino)-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

A mixture of sodium hydride (60% dispersion in mineral oil, 0.13 g) in DMF (5 ml) was stirred under ice-cooling for 5 min. and methyl 2-ethylamino-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate (0.95 g) was added to the mixture, followed by stirring for 10 min. To the mixture was added methyl iodide (0.2 ml) and the mixture was stirred for 20 min. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and evaporated to dryness. The residue was purified by column chromatography on silica gel to give crude crystals, which were recrystal-

lized from ethyl acetate - hexane to afford colorless needles (0.88 g, 82%), m.p. 66-69° C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.25(3H,t), 3.03(3H,s), 3.36(2H,q), 3.73(3H,s), 5.60(2H,s), 6.88(2H,d), 7.16(1H,t), 7.34-7.49(5H,m), 7.59(1H,dt), 7.73(1H,dd), 7.78(1H,dd)
IR(KBr) cm^{-1}: 2210, 1710, 1540, 1530, 1435, 1420, 1385, 1300, 1275, 1250, 1005, 760

Reference Example 9

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-oxo-2,3-dihydrobenzimidazole-7-carboxylate

To a solution of methyl 2-[(2'-cyanobiphenyl-4-yl)methylamino]-3-methoxycarbonylaminobenzoate (10.5 g) in methanol (100 ml) was added NaOMe (10 g), and the mixture was heated under reflux for 20 hours. The reaction mixture was neutralized with 1N-HCl and concentrated to dryness. The residue was extracted with chloroform - water. The organic layer was washed with water, dried and evaporated to dryness. The resulting crystals were recrystallized from chloroform - methanol to afford colorless needles (8.67 g, 89%), m.p. 250-253° C.
^{1}H-NMR(200MHz,DMSO-d_6) δ : 3.65(3H,s), 5.35(2H,s), 7.04-7. 16(3H,m), 7.24-7.28(2H,m), 7.48-7.59(4H,m), 7.76(1H,dt), 7.92(1H,dd)
IR(KBr) cm^{-1}: 2210, 1720, 1690, 1635, 1430, 1390, 1270, 1255, 760, 750, 730, 690

Reference Example 10

Methyl 2-chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

A mixture of methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-oxo-2,3-dihydrobenzimidazole-7-carboxylate (8.02 g) in phosphorus oxychloride (30 ml) was heated under reflux for 8 hours. The reaction mixture was concentrated and the resulting residue was poured into ice-water. The mixture was extracted with chloroform. The extract was washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel to give crystals, which were recrystallized from chloroform - methanol to afford colorless needles (2.2 g, 28%), m.p. 154-157° C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.78(3H,s), 5.95(2H,s), 7.06(2H,d), 7.31 (1H,t), 7.39-7.48(4H,m), 7.58-7.66-(1H,m), 7.71-7.77(2H,m), 7.93(1H,dd)
IR(KBr) cm^{-1}: 2240, 1720, 1480, 1450, 1440, 1425, 1370, 1350, 1290, 1270, 1200, 1150, 1120, 1000, 775, 760, 750

Reference Example 11

Methyl 2-[(2'-cyanobiphenyl-4-yl)methylamino]-3-methoxycarbonylaminobenzoate

To a stirred solution of methyl 3-amino-2-[(2'-cyanobiphenyl-4-yl)methylamino]benzoate (10 g) in pyridine (50 ml) was added dropwise methyl chloroformate (9.0 ml) under ice-cooling. The mixture was stirred at room temperature for 3 hours and concentrated. The residue was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate - hexane to afford pale yellow needles (10.5 g, 90%), m.p. 113-115° C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.80(3H,s), 3.83(3H,s), 4.11(2H,d), 6.29(1H,brs), 7.09(1H,t), 7.40-7.80(10H,m), 8.19(1H,d)

Working Example 14

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-morpholinobenzimidazole-7-carboxylate

A mixture of methyl 2-chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate (0.8 g) in morpholine (15 ml) was stirred at 100° C for 2 hours and the reaction mixture was concentrated to dryness. The residue was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The resulting crystals were recrystallized from ethyl acetate - hexane to afford colorless prisms (0.69 g, 77%).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.38(4H,t), 3.72(3H,s), 3.90(4H,t), 5.63(2H,s), 6.89(2H,d), 7.20(1H,t), 7.37-7.65-(6H,m), 7.74(1H,dd), 7.82(1H,dd)
IR(KBr) cm^{-1}: 2225, 1715, 1520, 1440, 1415, 1280, 1260, 1220, 1130, 1120, 1010, 860, 770, 760, 750

Working Example 15

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-piperidinobenzimidazole-7-carboxylate

The title compound was prepared in substantially the same manner as Working Example 14. Yield: 81%, m.p. 119-121 °C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.62-1.77(6H,m), 3.31-3.36(4H,m), 3.73(3H,s), 5.58(2H,s), 6.88(2H,d), 7. 15-(1H,t), 7.35-7.49(5H,m), 7.56-7.64(1H,m), 7.73(1H,dd), 7.79(1H,dd)
IR(KBr) cm^{-1}: 2225, 1720, 1530, 1445, 1410, 1385, 1305, 1285, 1265, 1250, 1130, 1110, 770, 750

Reference Example 12

Methyl 2-(2'-methoxycarbonylbiphenyl-4-yl)methylamino]-3-nitrobenzoate

To a solution of methyl 2-tert-butoxycarbonylamino-3-nitrobenzoate (1.84 g) in acetonitrile (10 ml) was added a solution of 4-(2'-methoxycarbonylbiphenyl-4-yl)methyl bromide (1.9 g) in acetonitrile (5 ml) and potassium carbonate (0.86 g) and the reaction mixture was heated under reflux for 20 hours. The reaction mixture was concentrated to dryness and the resulting residue was extracted with ethyl acetate and water. The organic layer was washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel to give pale yellow syrup. The syrup was dissolved in ethanol (10 ml) and 20% hydrochloric acid in ethanol (4 ml) was added to the solution. The reaction mixture was stirred at room temperature for 22 hours and concentrated to dryness. The residue was dissolved in ethyl acetate and the solution was washed with saturated aqueous sodium bicarbonate and water, dried and evaporated to afford yellow syrup (1.39 g, 53%).
^{1}H-NMR(200MHz,$CHCl_3$) δ : 3.61(3H,s), 3.89(3H,s), 4.21(2H,d), 6.72(1H,t), 7.30(4H,d), 7.36(1H,dd), 7.42-(1H,dd), 7.53(1H,dd), 7.82(1H,dd), 8.00(1H,dd), 8. 10(1H,dd)

Reference Example 13

Methyl 3-amino-2-[(2'-methoxycarbonylbiphenyl-4-yl)methylamino]benzoate

The title compound was prepared as pale yellow syrup from methyl 2-[(2'-methoxycarbonylbiphenyl-4-yl)methylamino]-3-nitrobenzoate in substantially the same manner as Working Example 2. Yield: 79%.
^{1}H-NMR(200MHz,$CHCl_3$) δ : 3.63(3H,s), 3.80(3H,s), 3.97(2H,brs), 4.22(2H,d), 6.40(1H,brs), 6.82-6.92(2H,m), 7.23-7.44(7H,m), 7.53(1H,dt), 7.79-7.83(1H,m)
IR(Neat)cm^{-1}: 3450, 3360, 2970, 1730, 1700, 1470, 1460, 1450, 1440, 1290, 1250, 1200, 770, 750

Working Example 16

Methyl 2-ethoxy-1-[(2'-methoxycarbonylbiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless plates from methyl 3-amino-2-[(2'-methoxycarbonylbiphenyl-4-yl)methylamino]benzoate in substantially the same manner as Working Example 4. Yield: 72%, m.p. 112-113 °C.
^{1}H-NMR(200MHz,$CHCl_3$) δ : 1.50(3H,t), 3.55(3H,s), 3.77(3H,s), 4.68(2H,q), 5.65(2H,s), 6.99(2H,d), 7. 17-(2H,d), 7. 17(1H,t), 7.31-7.55(4H,m), 7.73(1H,dd), 7.77(1H,dd)
IR(Neat)cm^{-1}: 1730, 1710, 1545, 1470, 1430, 1380, 1340, 1320, 1270, 1250, 1235, 1210, 1120, 1080, 1030, 750, 740, 710

Working Example 17

Methyl 2-butoxy-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless needles in substantially the same manner as Working Example 7. Yield: 75%, m.p. 74-75 °C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.95(3H,t), 1.35-1.54(2H,m), 1.77-1.90(2H,m), 3.76(3H,s), 4.60(2H,t), 5.69(2H,s), 7.10(2H,d), 7.17(1H,t), 7.43(4H,d), 7.54-7.65(2H,m), 7.74(2H,dd)
IR(KBr) cm^{-1}: 2220, 1725, 1560, 1490, 1470, 1440, 1395, 1320, 1295, 1265, 1245, 1120, 1050, 1020, 770

Working Example 18

Methyl 2-allyloxy-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless plates in substantially the same manner as Working Example 7. Yield: 73%, m.p. 118-119° C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.76(3H,s), 5.12(2H,m), 5.33(1H,m), 5.43(1H,m), 5.72(2H,s), 6.02-6.21(1H,m), 7.11(2H,d), 7.19(1H,t), 7.44(4H,d), 7.56-7.66(2H,m), 7.75(2H,dd)
IR(KBr) cm^{-1}: 2220, 1705, 1540, 1470, 1460, 1425, 1410, 1400, 1330, 1300, 1270, 1250, 1225, 1205, 1100, 1015, 995, 760, 750, 740, 730

Working Example 19

Methyl 2-ethylamino-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless crystals (3.2 g, 32%) according to the procedure for Working Example 8 from methyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-(3-ethylthioureido)benzoate (10.5 g), which was synthesized from methyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate in substantially the same manner as Reference Example 5.
^{1}H-NMR(200MHz,$CDCl_3$) δ: 1.24(3H,t), 3.49-3.63(2H,m), 4.06(1H,t), 5.55(2H,s), 7.16(1H,t), 7.27(2H,d), 7.41-7.79(8H,m)
IR(KBr) cm^{-1}: 3275, 2225, 1720, 1620, 1610, 1580, 1570, 1480, 1350, 1275, 1240, 1215, 1100, 1070, 770, 760

Working Example 20

2-Cyano-4'-methylbiphenyl

20a) N-(2-Methoxyphenyl)methylidenecyclohexylamine

A solution of anisaldehyde (21 g) and cyclohexylamine (15 g) in chloroform (100 ml) was stirred at room temperature for 2 hours and evaporated to afford brown syrup (35 g, quantitative).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.21-1.87(10H,m), 3.14-3.28(1H,m), 3.86(3H,s), 6.88-7.00(2H,m), 7.36(1H,m), 7.95(2H,dd), 8.75(1H,s)

20b) 4'-Methyl-2-biphenylcarbaldehyde

To a suspension of magnesium metal (1.1 g) in THF (3 ml) was added dropwise a solution of 4-bromotoluene (7.5 g) in THF (10 ml) under gentle reflux. The resulting solution of the Grignard reagent was added dropwise to an ice-cooled, stirred solution of N-(2-methoxyphenyl)methylidenecyclohexylamine (4.3 g) in THF (30 ml). The reaction mixture was stirred at room temperature for 1.5 hours, followed by heating under reflux for 7 hours. After addition of ice-water, the reaction mixture was acidified with conc. hydrochloric acid. The reaction mixture was extracted with ethyl acetate and the extract was washed with 1N-hydrochloric acid and water, dried and evaporated to dryness. The residue was purified by column chromatography on silica gel to give pale yellow syrup (2.0 g, 51%).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 2.43(3H,s), 7.28(4H,s), 7.42-7.51 (2H,m), 7.63(1H,t), 8.02(1H,d), 10.00(1H,s)

20c) 2-Cyano-4'-methylbiphenyl

A mixture of 4'-methyl-2-biphenylcarbaldehyde (2.0 g) and hydroxyamine hydrochloride (1.0 g) in pyridine (10 ml) was stirred at room temperature for 15 min., followed by addition of acetic anhydride (4.1 g). The reaction mixture was stirred at 90 - 100° C for 1 hr. and concentrated to dryness. After addition of water to the residue, the precipitated crystals were collected by filtration. Recrystallization from hexane gave colorless needles (1.5 g, 79%).
^{1}H-NMR(90MHz,$CDCl_3$) δ : 2.40(3H,s), 7.2-7.8(8H,m)
The title compound can be readily converted into Compound (IIIa') according to the known references as mentioned above.

Working Example 21

Methyl 2-carboxy-3-nitrobenzoate

To a suspension of 3-nitrophthalic acid (211 g) and methyl orthoformate (127 g) in methanol (420 ml) was added conc. sulfuric acid (20 ml) dropwise with stirring. The reaction mixture was heated under reflux for 18 hours and concentrated to dryness. After addition of water (30 ml) to the residue, the mixture was stirred at 3 - 10° C for one hour. The precipitated crystals were recrystallized from ethyl acetate - hexane to give pale yellow prisms (185 g, 82%), m.p. 166-168° C.
^{1}H-NMR(200MHz, $CDCl_3$) δ : 4.03(3H,s), 7.74(1H,t), 8.39(1H,dd), 8.42(1H,dd)

Working Example 22

Methyl 2-tert-butoxycarbonylamino-3-nitrobenzoate

To a solution of methyl 2-carboxy-3-nitrobenzoate (7.23 g) in DMF (50 ml) was added diphenylphosphoryl azide (11.3 g) at room temperature and then triethylamine (6.7 ml) was added dropwise to the stirred reaction mixture. After stirring at room temperature for 3 hours, tert-butanol (54 ml) was added to the stirred reaction mixture. After stirring at room temperature for 30 min., the reaction mixture was gradually warmed, then heated under reflux for 1 hour and evaporated to dryness. The resultant residue was dissolved in ethyl acetate, washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, and then dried. After evaporation of the solvent, methanol was added to the resultant residue and the mixture was cooled to give colorless crystals (6.7 g, 70%).
^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.50(9H,s), 3.96(3H,s), 7.23(1H,t), 8.10(1H,dd), 8.17(1H,dd)
IR(KBr) cm^{-1}: 3360, 1730, 1705, 1580, 1520, 1490, 1440, 1365, 1355, 1310, 1270, 1240, 1150, 870, 835, 770, 725, 705

Working Example 23

Methyl 2-[[N-tert-butoxycarbonyl-N-(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate

A solution of methyl 2-tert-butoxycarbonylamino-3-nitrobenzoate (0.6 g), 2-(4-bromomethylphenyl)-benzonitrile (0.54 g) and K_2CO_3 (0.28 g) in acetonitrile (10 ml) was heated under reflux for 4 hours and concentrated to dryness. Water was added to the resultant residue and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and evaporated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - hexane afforded colorless prisms (0.83 g, 85%), m.p. 153-154° C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.35(9H,s), 3.70(3H,s), 4.63(1H,d), 4.80(1H,d), 7.23-7.29(3H,m), 7.39-7.53(6H,m), 7.59-7.67(1H,m), 7.75(1H,dd), 7.93(1H,dd), 7.99(1H,dd), 8.05(1H,dd), 8.11 (1H,dd)
IR(KBr) cm^{-1}: 2220, 1700, 1530, 1390, 1360, 1315, 1290, 1160, 765

Working Example 24

Methyl 2-[[2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate

A mixture of methyl 2-[[N-tert-butoxycarbonyl-N-(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate (0.49 g) in 20% HCl-ethanol (3 ml) and ethyl acetate (3 ml) was stirred at room temperature for 1 hour. After evaporation of the solvent, to the residue was added methanol and saturated aqueous sodium bicarbonate to give crystals. The crystals were collected by filtration and recrystallized from chloroform - methanol to give pale yellow crystals (0.3 g, 77%), m.p. 140-141° C.
^{1}H-NMR(200MHz, DMSO-d_6) δ : 3.84(3H,s),. 4.26(2H,m), 6.86(1H,t), 7.46(2H,d), 7.54-7.65(4H,m), 7.79(1H,d), 7.95(dd), 8.05-8.11 (2H,m), 8.67(1H,t)

Working Example 25

Methyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate

A mixture of methyl 2-[[2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate (10 g), $FeCl_3 \cdot 6H_2O$ (0.1

g), activated charcoal (1 g) in a mixture of methanol (100 ml) and THF (50 ml) was heated under reflux for 30 min. Hydrazine hydrate (7.2 ml) was added dropwise to the reaction mixture and the mixture was then heated under reflux for 14 hours. The insoluble material was removed from the reaction mixture by filtration and the filtrate was concentrated. to dryness. Aqueous sodium bicarbonate was added to the resulting residue and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and evaporated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization from isopropyl ether afforded pale yellow needles (6.0 g, 64%), m.p. 110-111 °C.
^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.81 (3H,s), 3.97(2H,brs), 4.23(2H,d), 6.39(1H,t), 6.84-6.93(2H,m), 7.26-7.55-(8H,m), 7.64(1H,dt), 7.77(1H,dd)

Working Example 26

Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-(2,2,2-trifluoroethoxy) benzimidazole-7-carboxylate

The title compound was prepared as pale yellow crystals from methyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate and 2,2,2-trifluoroethyl orthocarbonate according to the procedure for Working Example 3. Yield: 25%, m.p. 143-145 °C.

Elemental Analysis for $C_{25}H_{18}F_3N_3O_3$:

	C(%)	H(%)	N(%)
Calcd.:	64.52;	3.90;	9.03
Found:	64.35;	3.95;	8.98

^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.80(3H,s), 5.01 (2H,q), 5.74(2H,s), 7.13(2H,d), 7.23(1H,t), 7.38-7.47(4H,m), 7.58-7.66(2H,m), 7.72-7.78(2H,m)
IR(KBr) cm^{-1}: 2225, 1735, 1550, 1465, 1430, 1305, 1280, 1270, 1250, 1170, 1060, 770, 750, 745

Working Example 27

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate

To a solution of ethyl 2-chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate (1.0 g) in ethanol (30 ml) was added NaOEt (0.17 g) and the mixture was heated under reflux for 1 hour. The reaction mixture was concentrated to dryness.
The resultant residue was dissolved in ethyl acetate and the solution was washed with water, and then dried. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give the title compound as colorless crystals(0.37 g, 70%).
^{1}H-NMR and IR spectra indicate that the product according to this Working Example is completely identical with that obtained in Working Example 4.

Reference Example 14

2-(4-Formylphenyl)benzonitrile

A mixture of 2-(4-bromomethylphenyl)benzonitrile (12 g) and sodium bicarbonate (26 g) in dimethyl sulfoxide (150 ml) was heated at 120 °C for 5 hours with stirring. After addition of water, the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization from chloroform - isopropyl ether gave colorless needles (5.77 g, 63%).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 7.49-7.58(2H,m), 7.67-7.84(4H,m), 8.00-8.05(2H,m), 10.10(1H,s)

Reference Example 15

2-(4-Aminomethylphenyl)benzonitrile

A mixture of 2-(4-bromomethylphenyl)benzonitrile (12 g) and potassium phtalimide (15 g) in DMF (200 ml) was stirred at 70° C for 5 hours. After addition of water, the mixture was extracted with methylene chloride. The extract was washed with water, dried and concentrated to dryness to give crystals. Recrystallization from ethyl acetate - isopropyl ether gave colorless crystals.
To a suspension of the crystals in methanol (500 ml) was added hydrazine hydrate (10 ml) and the mixture was refluxed for 12 hours. After evaporation of the solvent, the residue was dissolved in ethyl acetate and the solution was washed with 1N-NaOH and water. The organic layer was dried and concentrated to dryness to give crystals (14.2 g, 93%).
^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.56(2H,brs), 3.88(2H,s),7.27-7.78(8H,m)

Working Example 28

Ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

A mixture of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate (0.7 g) and trimethyltin azide (0.7 g) in toluene (15 ml) was heated under reflux for 4 days. The reaction mixture was concentrated to dryness and to the residue were added methanol (20 ml) and 1N-HCl (10 ml). The mixture was stirred at room temperature for 30 minutes and adjusted to pH 3 to 4 with 1N NaOH. After removal of the solvent, the residue was partitioned between chloroform and water. The organic layer was washed with water and dried, and the solvent was evaporated to dryness to give a syrup. The syrup was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (0.35 g, 45%), m.p. 158-159° C.

Elemental Analysis for $C_{28}H_{24}N_6O_3$:

	C(%)	H(%)	N(%)
Calcd.:	66.65;	5.16;	17.94
Found :	66.61;	5.05;	17.84

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.09(3H,t), 1.43(3H,t), 4.02(2H,q), 4.30(2H,q), 5.57(2H,s), 6.71(2H,d), 6.83-6.96-(4H,m), 7.27-7.31 (1H,m), 7.40(1H,dd), 7.55-7.66(2H,m), 8.04-8.09(1H,m)
IR(KBr) cm^{-1}: 1720, 1605, 1540, 1470, 1430, 1250, 1040, 750

Working Example 29

2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

A solution of ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.24 g) and 1N NaOH (1.5 ml) in ethanol (4 ml) was stirred at 80° C for one hour. The reaction mixture was concentrated, and the concentrate was extracted with water and ethyl acetate. The aqueous layer was adjusted to pH 3-4 with 1N-HCl to give crystals. Recrystallization of the crystals from ethyl acetate - methanol afforded colorless crystals (0.15 g, 67%); m.p. 183-185° C.

Elemental Analysis for $C_{24}H_{20}N_6O_3.1/5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	64.91;	4.63;	18.93
Found :	65.04;	4.51;	18.77

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.38(3H,t), 4.58(2H,q), 5.63(2H,s), 6.97(4H,q), 7.17(1H,t), 7.47-7.68(6H,m)
IR(KBr) cm^{-1}: 1710, 1550, 1480, 1430, 1280, 1240, 1040, 760

Working Example 30

Ethyl 2-propoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

A mixture of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-propoxybenzimidazole-7-carboxylate (0.69 g) and trimethyltin azide (0.7 g) in toluene (15 ml) was heated for 4 days under reflux. The reaction mixture was concentrated to dryness and to the mixture was added methanol (20 ml) and 1N-HCl (10 ml). After stirring at room temperature for 30 minutes, the mixture was adjusted to pH 3-4 with 1N NaOH. After removal of the solvent, the residue was extracted with chloroform-water. The organic layer was washed with water and dried, and the solvent was evaporated to dryness to give a syrup. The syrup was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (0.31 g, 43%), m.p. 157-159° C.

Elemental Analysis for $C_{27}H_{26}N_6O_3$:

	C(%)	H(%)	N(%)
Calcd.:	67.21;	5.43;	17.42
Found :	67.26;	5.45;	17.28

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.03(3H,t), 1.13(3H,t), 1.75-1.92(2H,m), 4.05(2H,q), 4.23(2H,q), 5.57(2H,s), 6.75-(2H,d), 6.90(2H,d), 6.96(2H,d), 7.28-7.33(1H,m), 7.39-7.44(2H,m), 7.57-7.62(2H,m), 8.07-8.11(1H,m)
IR(KBr) cm^{-1}: 1720, 1540, 1470, 1430, 1280, 1250, 1130, 1020, 750

Working Example 31

2-Propoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

A solution of ethyl 2-propoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.23 g) in ethanol (4 ml) containing 1N-NaOH (1.5 ml) was heated at 80° C for 2 hours. The reaction mixture was concentrated to dryness and the residue was extracted with water and ethyl acetate. The aqueous layer was adjusted to pH 3-4 with 1N-HCl to give crystals. Recrystallization from ethyl acetate - methanol afforded colorless crystals (0.15 g, 69%), m.p. 174-175° C.

Elemental Analysis for $C_{25}H_{22}N_6O_3.0.3H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	65.29;	4.95;	18.27
Found :	65.41;	4.92;	18.20

^{1}H-NMR(200MHz,DMSO-d_6) δ : 0.92(3H,t), 1.70-1.87(2H,m), 4.47(2H,q), 5.63(2H,s), 6.96(4H,dd), 7.16(1H,t), 7.42-7.67(6H,m)
IR(KBr) cm^{-1}: 1700, 1550, 1430, 1290, 1240, 765

Working Example 32

Ethyl 2-mercapto-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

A mixture of ethyl [1-(2'-cyanobiphenyl-4-yl)methyl]-2-mercaptobenzimidazole-7-carboxylate (4.1 g) and trimethyltin azide (8.0 g) in toluene (100 ml) was heated for 4 days under reflux. The solvent was evaporated to dryness and the residue was stirred in a mixture of conc. hydrochloric acid (2 ml) and methanol (20 ml) at room temperature for 20 minutes. To the reaction mixture was added 1N-NaOH to adjust to about pH 4 and then the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried, and concentrated to dryness to give crystals. Recrystallisation from chloroform gave colorless crystals (5.0 g, 89%), m.p. 263-264° C (decomp.).

Elemental Analysis for $C_{24}H_{20}N_6O_2S.1/2H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	61.92;	4.55;	18.05
Found :	61.99;	4.30;	17.86

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.10(3H,t), 4.09(2H,q), 5.82(2H,br s), 6.87(2H,d), 7.00(2H,d), 7.26(1H,t), 7.37-7.69(6H,m)
IR(KBr) cm^{-1}: 1720, 1460, 1440, 1365, 1340, 1260, 1180, 1145, 1150, 1110, 990, 745

Working Example 33

Ethyl 2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

To a solution of ethyl 2-mercapto-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]benzimidazole-7-carboxylate (0.68 g) in ethanol (10 ml) containing 1N-NaOH (3.0 ml) was added methyl iodide (0.24 g), and the mixture was stirred at room temperature for 2 hours.
The reaction mixture was neutralized with dilute hydrochloric acid to give crystals. The crystals were purified by column chromatography on silica gel. Recrystallization from ethyl acetate afforded colorless prisms (0.31 g, 44%), m.p. 207-208° C (decomp.).

Elemental Analysis for $C_{25}H_{22}N_6O_2S$:

	C(%)	H(%)	N(%)
Calcd.:	63.81;	4.71;	17.86
Found :	63.55;	4.81;	17.50

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.13(3H,t), 2.77(3H,s), 4.14(2H,q), 5.62(2H,s), 6.84(2H,d), 7.26(1H,t), 7.46-7.70(5H,m)
IR(KBr) cm^{-1}: 1705, 1480, 1450, 1420, 1360, 1340, 1275, 1255, 1190, 1140, 1100, 1025, 990, 770, 750

Working Example 34

Ethyl 2-ethylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

To a solution of ethyl 2-mercapto-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.91 g) in ethanol (13 ml) containing 1N-NaOH (4 ml) was added ethyl iodide (0.34 g), and the mixture was stirred at room temperature for 4 hours. The reaction mixture was adjusted to pH 4 with dilute hydrochloric acid to give crystals. The crystals were collected by filtration and purified by column chromatography on silica gel. Recrystallization from ethyl acetate gave colorless prisms (0.55 g, 57%), m.p. 153-154° C (decomp.).

Elemental Analysis for $C_{26}H_{24}N_6O_2S$:

	C(%)	H(%)	N(%)
Calcd.:	64.44;	4.99;	17.34
Found :	64.37;	5.05;	17.20

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.19(3H,t), 1.37(3H,t), 3.20(2H,q), 4.12(2H,q), 5.67(2H,s), 6.75(2H,d), 6.92(2H,d), 7.05(1H,t), 7.26-7.34(2H,m), 7.50(1H,dd), 7.53-7.63(2H,m), 8.05-8.11 (1H,m)
IR(KBr) cm^{-1}: 1715, 1450, 1420, 1365, 1345, 1280, 1195, 1145, 1110, 1035, 1015, 990, 760, 745

Working Example 35

Ethyl 2-propylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]benzimidazole-7-carboxylate

Propyl iodide (0.37 g) was added to a solution of ethyl 2-mercapto-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate (0.91 g) in ethanol (13 ml) containing 1N NaOH (4.0 ml) and the mixture was stirred at room temperature for 5 hours. The reaction mixture was adjusted to about pH 4 with dilute hydrochloric acid to give crystals. The crystals were collected by filtration and purified by column chromatography on silica gel. Recrystallization from ethyl acetate - hexane gave colorless prisms (0.4 g, 40%), m.p. 177-178° C (decomp.).

Elemental Analysis for $C_{27}H_{26}N_6O_2S$:

	C(%)	H(%)	N(%)
Calcd.:	65.04;	5.26;	16.85
Found :	64.88;	5.25;	16.78

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.04(3H,t), 1.19(3H,t), 1.76(2H,m), 3.18(2H,t), 4.12(2H,q), 5.69(2H,s), 6.75(2H,d), 6.93(2H,d), 7.05(1H,t), 7.27-7.34(2H,m), 7.50(1H,dd), 7.54-7.63(2H,m), 8.07-8.12(1H,m)
IR(KBr) cm^{-1}: 1715, 1450, 1420, 1380, 1365, 1350, 1280, 1260, 1190, 1145, 1035, 1020, 990, 760, 745

Working Example 36

2-Methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

A solution of ethyl 2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.2 g) in a methanol (5 ml) solution containing 1N NaOH (1.3 ml) was heated under reflux for 2 hours. The reaction mixture was adjusted to about pH 4 with dilute hydrochloric acid to give crystals. The crystals were collected by filtration, and recrystallized from ethyl acetate - hexane to give colorless crystals (0.17 g, 81%), m.p. 223-225° C (decomp.).

Elemental Analysis for $C_{23}H_{18}N_6O_2S.1/2C_8H_8O_2$

	C(%)	H(%)	N(%)
Calcd.:	61.72;	4.56;	17.27
Found :	61.59;	4.54;	17.54

^{1}H-NMR(200MHz,DMSO-d_6) δ : 2.75(3H,s), 5.76(2H,s), 6.88(2H,d), 7.01(2H,d), 7.25(1H,t), 7.47-7.66(5H,m), 7.82(1H,d)
IR(KBr) cm^{-1}: 1710, 1485, 1450, 1420, 1370, 1345, 1320, 1280, 1245, 1195, 1150, 990, 780, 760

Working Example 37

2-Ethylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

A solution of ethyl 2-ethylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.35 g) in a methanol (7 ml) solution containing 1N NaOH (2.2 ml) was heated under reflux for 2 hours. After evaporation of the solvent, the aqueous residue was adjusted to about pH 3-4 with 1N-HCl to give crystals. The crystals were collected by filtration. Recrystallization from ethyl acetate - methanol gave colorless crystals (0.21 g, 64%), m.p. 209-210° C (decomp.).

Elemental Analysis for $C_{24}H_{20}N_6O_2S$:

	C(%)	H(%)	N(%)
Calcd.:	63.14;	4.42;	18.41
Found :	62.89;	4.35;	18.15

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.39(3H,t), 3.36(2H,q), 5.76(2H,s), 6.87(2H,d), 7.01 (2H,d), 7.25(1H,t), 7.47-7.69(5H,m), 7.82(1H,dd)
IR(KBr) cm^{-1}: 1695, 1450, 1415, 1350, 1275, 1225, 1190, 1180, 1145, 755, 740

Working Example 38

2-Propylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

A solution of ethyl 2-propylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.25 g) in methanol (5 ml) containing 1N-NaOH (1.5 ml) was heated under reflux for 2 hours. After removal of the solvent, the aqueous residue was adjusted to about pH 3-4 with 1N-HCl to give crystals. The crystals were collected by filtration. Recrystallization from ethyl acetate - hexane gave colorless crystals (0.21 g, 91%), m.p. 222-223° C (decomp.).

Elemental Analysis for $C_{25}H_{21}N_6O_2S$:

	C(%)	H(%)	N(%)
Calcd.:	63.95;	4.51;	17.90
Found :	63.78;	4.85;	17.59

^{1}H-NMR(200MHz,DMSO-d_6) δ : 0.99(3H,t), 1.67-1.85(2H,m), 3.35(2H,t), 5.77(2H,s), 6.87(2H,d), 7.01 (2H,d), 7.25(1H,t), 7.46-7.70(5H,m), 7.82(1H,dd)
IR(KBr) cm^{-1}: 1700, 1450, 1280, 1240, 1195, 1145, 755, 740

Working Example 39

Methyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

A mixture of methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate (1.85 g) and trimethyltin azide (2.80 g) in toluene (15 ml) were heated under reflux for one day. The reaction mixture was concentrated to dryness. To the residue were added methanol (50 ml) and 1N-HCl (20 ml) and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was adjusted to about pH 3-4 with 1N-NaOH. After removal of the solvent, the residual syrup was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - benzene gave colorless crystals (1.16 g, 56%), m.p. 191-193° C (decomp.).

Elemental Analysis for $C_{25}H_{22}N_6O_3.1/5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	65.58;	4.75;	18.53
Found :	65.55;	4.93;	18.35

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1 .43(3H,t,J=7.0Hz)), 3.57(3H,s), 4.30(2H,q,J=7.oHz), 5.54(2H,s), 6.72-(2H,d,J=8.2), 6.84-6.97(4H,m), 7.28-7.33(1H,m), 7.40(1H,dd,J=1.8,7.0Hz), 7.57-7.62(2H,m), 8.03-8.07-(1H,m)

IR(KBr) cm^{-1}: 1720, 1550, 1475, 1430, 1280, 1250, 1040, 755, 735

Working Example 40

Ethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-carboxylate

A mixture of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethylaminobenzimidazole-7-carboxylate (1.23 g) and trimethyltin azide (2.80 g) in toluene (15 ml) was heated for 40 hours under reflux. Precipitates were collected by filtration and suspended in methanol (50 ml). To the suspension was added 1N-HCl (15 ml), and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was adjusted to about pH 5 with 1N-NaOH, followed by extraction with chloroform. The organic layer was washed with water, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallisation from methanol - ethyl acetate gave colorless crystals (0.83 g, 61%), m.p. 166-168° C.

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.13(3H,t), 1.21 (3H,t), 343(2H,q), 4.13(2H,q), 5.48(2H,s), 6.78(2H,d), 6.99(2H,d), 7.07(1H,t), 7.22(1H,dd), 7.42-7.49(2H,m), 7.54-7.69(3H,m)

IR(KBr) cm^{-1}: 1720, 1650, 1310, 1285, 765, 755, 750

Working Example 41

Ethyl 2-propylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

A solution of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-propylaminobenzimidazole-7-carboxylate (1.20 g) and trimethyltin aside (2.7 g) in toluene (15 ml) was heated for 50 hours under reflux. Precipitates were collected by filtration and suspended in methanol (20 ml). After addition of 1N-HCl (15 ml), the reaction mixture was stirred at room temperature for 10 minutes. The mixture was adjusted to about pH 5 with 1N-NaOH, followed by extraction with chloroform. The organic layer was washed with water, dried and concentrated to dryness. The concentrate was purified by column chromatography on silica gel to give crystals. Recrystallization from methanol - ethyl acetate gave colorless crystals (10 g, 77%), m.p. 170-172° C.

^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.89(3H,t), 1.14(3H,t), 1.52-1.70(2H,m), 3.35(2H,t), 4.14(2H,q), 5.49(2H,s), 6.77-(2H,d), 6.99(2H,d), 7.05(1H,t), 7.21 (1H,dd), 7.39-7.47(2H,m), 7.50-7.65(3H,m)

IR(KBr) cm^{-1}: 1720, 1670, 1660, 1290, 1270, 760

Working Example 42

2-Ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

To a solution of 2-ethoxy-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (2.07 g) in methylene chloride (10 ml) were added trityl chloride (1.59 g) and triethylamine (0.8 ml). The mixture was stirred at room temperature for one hour. The reaction mixture was washed with water, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization of crude crystals thus obtained from ethyl acetate - benzene gave colorless crystals (2.12 g, 66%), m.p. 168-170° C.

Elemental Analysis for $C_{43}H_{34}N_6O_3$:

	C(%)	H(%)	N(%)
Calcd.:	75.64;	5.02;	12.31
Found :	75.37;	4.96;	12.20

^{1}H-NMR(200MHz,$CDCl_3$) δ: 1.40(3H,t), 4.61(2H,q), 5.58(2H,s), 6.76(2H,d), 6.91-6.96(8H,m), 7.12(1H,t), 7.17-7.41(12H,m), 7.60(1H,dd), 7.73-7.82(2H,m)

Working Example 43

Pivaloyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]benzimidazole-7-carboxylate

To a solution of 2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (2.2 g) in DMF (10 ml) were added potassium carbonate (0.53 g) and pivaloyloxymethyl iodide (0.94 g), and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the residue was dissolved in methanol (30 ml) and 1N-HCl (6 ml). The mixture was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the residue was purified by column chromatography on silica gel to give crystals. The crystals were recrystallized from ethyl acetate - hexane to give colorless crystals (1.13 g, 63%), m.p. 104-106 °C.

Elemental Analysis for $C_{30}H_{30}N_6O_5 \cdot 1/5C_4H_8O_2 \cdot 1/5C_6H_{14}$:

	C(%)	H(%)	N(%)
Calcd.:	65.06;	5.90;	14.32
Found :	64.79;	5.85;	14.43

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.13(9H,s), 1.44(3H,t), 4.37(2H,q), 5.61 (2H,s), 5.68(2H,s), 6.80(2H,d), 6.93-(2H,d), 6.99-7.11 (2H,m), 7.33-7.37(1H,m), 7.49-7.54(1H,m), 7.59-7.62(2H,m), 8.03-8.07(1H,m)

Working Example 44

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

To a solution of 2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (0.5 g) in DMF (5 ml) were added potassium carbonate (0.12 g) and cyclohexyl 1-iodoethyl carbonate (0.26 g). The mixture was stirred for one hour at room temperature. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the residue was dissolved in methanol (10 ml) and to the solution was added 1N-HCl (2 ml). The mixture was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and dried. After removal of the solvent, the residue was purified by column chromatography on silica gel to give colorless powder (0.21 g, 47%), m.p. 103-106 °C.

Elemental Analysis for $C_{33}N_{34}N_6O_6$:

	C(%)	H(%)	N(%)
Calcd:	64.91;	5.61;	13.76
Found :	64.94;	5.71;	13.66

To the powder (1 g) obtained as above was added ethanol (6 ml). The mixture was stirred for 3 hours at room temperature and allowed to stand under ice-cooling. The mixture was then stirred for one hour at temperatures not higher than 10 °C. Resultant crystals were collected by filtration and washed with cold ethanol. The crystals were dried at 25 °C for 9 hours under reduced pressure, then at 35 °C for further 18 hours to obtain white powdery crystals (0.94 g), m.p. 158-166 °C (decomp.).

Elemental Analysis for $C_{33}H_{34}N_6O_6$:

	C(%)	H(%)	N(%)
Calcd.:	64.91;	5.61;	13.76
Found :	64.73;	5.66;	13.64

^{1}H-NMR (200MHz) δ : 1.13-1.84(16H,m), 4.28-4.55(3H,m), 5.65(2H,d), 6.72(1H,q), 6.81(2H,d), 6.93(2H,d), 7.03(1H,t), 7.22-7.23(1H,m), 7.31-7.36(1H,m), 7.52-7.60(3H,m), 8.02-8.07(1H,m)
IR(KBr) cm^{-1}: 2942, 1754, 1717, 1549, 1476, 1431, 1076, 1034, 750
MS(m/z) : 611 $[M+H]^+$

Working Example 45

Methyl 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Methyl [1-(2'-cyanobiphenyl-4-yl)methyl]-2-methoxybenzimidazole-7-carboxylate (0.60 g) and trimethyltin azide (1.5 g) in toluene (15 ml) were heated for 40 hours under reflux. Precipitated crystals were dissolved in methanol (10 ml) and to the solution was added 1N-HCl (3 ml). The mixture was stirred for 10 minutes at room temperature and the methanol was evaporated.
The aqueous residue was adjusted to pH 3-4 with 1N-NaOH, followed by extraction with ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the residue was purified by column chromatography on silica gel to give crystals. The crystals were recrystallized from ethyl acetate to give colorless prisms (0.65 g, 65%), m.p. 165-166 °C.

Elemental Analysis for $C_{24}H_{20}N_6O_3.1/10H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	65.18;	4.60;	19.00
Found :	64.91;	4.49;	18.99

^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.64(3H,s), 3.93(3H,s), 5.55(2H,s), 6.75(2H,d), 6.90-7.01(4H,m), 7.31-7.36(1H,m), 7.49(1H,dd), 7.55-7.64(2H,m), 8.03-8.07(1H,m)

Working Example 46

2-Methoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

To a solution of methyl 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.22 g) in methanol (10 ml) was added 1N-NaOH (1.5 ml). The mixture was heated for 6 hours under reflux. The reaction mixture was concentrated to dryness and to the residue was added water. The mixture was adjusted to pH 3-4 with 1N-HCl to give crystals. Recrystallization from methanol-chloroform gave colorless needles (0.17 g, 77%), m.p. 208-209 °C.

Elemental Analysis for $C_{23}H_{18}N_6O_3.0.7H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	62.92;	4.45;	19.14
Found :	62.81;	4.08;	19.19

^{1}H-NMR(200MHz,DMSO-d_6) δ : 4.15(3H,s), 5.63(2H,s), 6.90(2H,d), 7.00(2H,d), 7.18(1H,t), 7.46-7.70(6H,m)

Working Example 47

2-Ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

To a solution of ethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]benzimidazole-7-carboxylate (0.52 g) in ethanol (5 ml) was added 1N-NaOH (4 ml), and the mixture was stirred for 2 hours at 80° C. The reaction mixture was concentrated to dryness and the aqueous residue was adjusted to pH 4-5 with 1N-HCl to give crystals. The crystals were collected by filtration and recrystallized from methanol-chloroform to give colorless crystals (0.3 g, 63.4%), m.p. 240-242° C.

Elemental Analysis for $C_{24}H_{21}N_7O_2 \cdot 1.1H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	62.76;	5.09;	21.35
Found :	62.65;	5.15;	21.23

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.20(3H,t), 3.43(2H,q), 5.62(2H,s), 6.85(2H,d), 6.99(2H,d), 7.10(1H,t), 7.34-(1H,d), 7.44-7.68(5H,m)

Working Example 48

2-Propylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

In substantially the same manner as Working Example 47, the above compound was obtained in a yield of 73%, m.p. 244-246° C.

Elemental Analysis for $C_{26}H_{23}N_7O_2 \cdot 1/2H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	64.92;	5.23;	21.20
Found :	64.79;	5.27;	21.08

In substantially the same manner as Working Example 43, the following compounds (Working Examples 49-53) were synthesized.

Working Example 49

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate

Yield: 55%, m.p. : 122-125° C (decomp.)

Elemental Analysis for $C_{29}H_{24}N_6O_6 \cdot CHCl_3$:

	C(%)	H(%)	N(%)
Calcd.:	53.63;	3.75;	12.51
Found :	53.32;	3.58;	12.24

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.43(3H,t), 2.11 (3H,s), 4.40(2H,q), 4.80(2H,s), 5.58(2H,s), 6.79(2H,d), 6.94-(2H,d), 7.02(1H,t), 7.15(1H,dd), 7.35-7.39(1H,m), 7.49-7.63(3H,m), 8.00-8.04(1H,m)

Working Example 50

Acetoxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 38%, m.p.: 152-154° C (decomp.)

Elemental Analysis for $C_{27}H_{24}N_6O_5$:

	C(%)	H(%)	N(%)
Calcd.:	63.27;	4.72;	16.40
Found :	63.55;	4.70;	16.18

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.43(3H,t), 2.01 (3H,s), 4.33(2H,q), 5.61(2H,s), 5.69(2H,s), 6.81(2H,d), 6.93-(2H,d), 7.01(1H,t), 7.13(1H,d), 7.33-7.38(1H,m), 7.53-7.62(3H,m), 8.03-8.07(1H,m)

Working Example 51

Propionyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 60%, m.p.: 145-150° C (decomp.)

Elemental Analysis for $C_{28}H_{26}N_6O_5 \cdot 0.2C_7H_8$:

	C(%)	H(%)	N(%)
Calcd.:	64.79;	5.10;	15.42
Found :	64.70;	5.10;	15.44

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.04(3H,t), 1.44(3H,t), 2.29(2H,q), 4.40(2H,q), 5.61(2H,s), 5.71(2H,s), 6.82(2H,d), 6.92-7.14(3H,m), 7.20(1H,m), 7.33-7.38(1H,m), 7.53-7.61(3H,m), 8.03-8.08(1H,m)

Working Example 52

Butyryloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 36%, m.p.: 96-100° C

Elemental Analysis for $C_{29}H_{28}N_6O_5 \cdot 0.4C_7H_8$:

	C(%)	H(%)	N(%)
Calcd.:	66.15;	5.45;	14.55
Found :	66.11;	5.44;	14.65

^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.85(3H,t), 1.44(3H,t), 1.55(2H,m), 2.24(2H,q), 4.38(2H,q), 5.61 (2H,s), 5.70-(2H,s), 6.81 (2H,d), 6.93(2H,d), 7.00(1H,t), 7.20(1H,m), 7.33-7.38(1H,m), 7.52-7.61 (3H,m), 8.01-8.10(1H,m)

Working Example 53

Isobutyryloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 53%, m.p.: 143-145° C

Elemental Analysis for $C_{29}H_{28}N_6O_5 \cdot 0.1C_7H_8$:

	C(%)	H(%)	N(%)
Calcd.:	64.88;	5.28;	15.29
Found :	65.04;	5.25;	15.18

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.09(6H,d), 1.44(3H,t), 2.50(1H,m), 4.38(2H,q), 5.61 (2H,s), 5.70(2H,s), 6.81 (2H,d), 6.91-7.00(3H,m), 7.19(1H,m), 7.33-7.37(1H,m), 7.51-7.63(3H,m), 8.02-8.07(1H,m)

In substantially the same manner as Working Example 44, the following compounds (Working Examples 54-56) were synthesized.

Working Example 54

1-(Ethoxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 44%, m.p.: 85-87°C

Elemental Analysis for $C_{29}H_{28}N_6O_6 \cdot 0.3H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	61.98;	5.13;	14.95
Found :	62.11;	5.02;	14.69

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.20(3H,t), 1.30(3H,d), 1.41 (3H,t), 4.03-4.22(3H,m), 4.31-4.47(1H,m), 5.61 (2H,s), 6.62-6.72(3H,m), 6.80-6.95(4H,m), 7.29-7.32(1H,m), 7.47(1H,dd), 7.54-7.64(2H,m), 7.97-8.01(1H,m)

Working Example 55

1-Acetoxyethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 31%, m.p.: 105-107°C

Elemental Analysis for $C_{28}H_{26}N_6O_5 \cdot 0.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	62.80;	5.08;	15.69
Found :	62.77;	4.69;	15.85

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.46(3H,t), 1.49(3H,d), 4.47-4.62(2H,m), 5.59(1H,d), 5.83(1H,d), 6.84(1H,q), 6.90-(2H,d), 7.03(2H,d), 7.11(1H,t), 7.34-7.39(1H,m), 7.49(1H,d), 7.53-7.61 (3H,m), 8.07-8.11(1H,m)

Working Example 56

1-(Isopropoxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 33%, m.p.: 74-76°C

Elemental Analysis for $C_{30}H_{30}N_6O_5.1.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	61.95;	5.72;	14.45
Found :	62.02;	5.43;	14.20

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.20(3H,d), 1.21 (3H,d), 1.30(3H,d), 1.42(3H,t), 4.08-4.24(1H,m), 4.34-4.50-(1H,m), 4.79(1H,m), 5.61 (2H,s), 6.62-6.75(3H,m), 7.27-7.32(1H,m), 7.48(1H,dd), 7.54-7.64(2H,m), 7.98-8.03-(1H,m)

Working Example 57

2-Methylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

The above compound was synthesized by substantially the same manner as Working Examples 40 and 47.

Yield: 40%, m.p.: 247-250° C (decomp.)

Elemental Analysis for $C_{23}H_{19}N_7O_2.2.0H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	59.86;	5.02;	21.25
Found :	59.99;	4.89;	21.36

^{1}H-NMR(200MHz,$CDCl_3$) δ : 2.94(3H,s), 5.64(2H,s), 6.82(2H,d), 6.99(2H,d), 7.02(1H,t), 7.31 (1H,d), 7.42-7.63-(5H,m)

In substantially the same manner as Working Example 43, the following compounds (Working Examples 58-60) were synthesized.

Working Example 58

Cyclohexylcarbonyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 54%, m.p.: 140-142° C

Elemental Analysis for $C_{32}H_{32}N_6O_5$:

	C(%)	H(%)	N(%)
Calcd.:	66.19;	5.55;	14.47
Found :	65.93;	5.46;	14.39

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.21-1.87(13H,m), 2.20-2.32(1H,m), 4.47(2H,q), 5.60(2H,s), 5.73(2H,s), 6.86-(2H,d), 7.07(1H,t), 7.27-7.40(3H,m), 7.54-7.61(2H,m), 8.05-8.09(1H,m)

Working Example 59

Benzoyloxymethyl 2-ethoxy-1-[[2'-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 47%, m.p.: 138-142° C

Elemental Analysis for $C_{32}H_{26}N_6O_5 \cdot 0.5H_2O \cdot 0.1C_4H_8O_2$:

	C(%)	H(%)	N(%)
Calcd.:	65.67;	4.76;	14.18
Found :	65.71;	4.66;	13.96

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.43(3H,t), 4.36(2H,q), 5.60(2H,s), 5.98(2H,s), 6.74(4H,s), 6.99(1H,t), 7.09-7.14-(1H,m), 7.21-7.36(3H,m), 7.50-7.59(4H,m), 7.90(2H,d), 8.02-8.06(1H,m)

Working Example 60

(E)-Cinnamoyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 56%, m.p.: 146-147°C

Elemental Analysis for $C_{34}H_{28}N_6O_5 \cdot 0.4C_4H_8O_2$:

	C(%)	H(%)	N(%)
Calcd.:	67.16;	5.07;	13.20
Found :	66.97;	4.86;	13.28

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.44(3H,t), 4.45(2H,q), 5.61(2H,s), 5.87(2H,s), 6.33(1H,d), 6.84(2H,d), 6.96(2H,d), 7.05(1H,t), 7.31-7.57(10H,m), 7.65(1H,d), 8.00-8.04(1H,m)

In substantially the same manner as Working Examples 43 and 44, the following compounds (Working Examples 61-63) were synthesized.

Working Example 61

Cyclopentylcarbonyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 54%, m.p.: 136-138°C

Elemental Analysis for $C_{31}H_{30}N_6O_5$:

	C(%)	H(%)	N(%)
Calcd.:	65.71;	5.34;	14.83
Found :	65.59;	5.33;	14.67

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.41-1.84(11H,m), 2.61-2.76(1H,m), 4.43(2H,q), 5.61 (2H,s), 5.72(2H,s), 6.84-(2H,d), 6.96(2H,d), 7.05(1H,t), 7.22-7.26(1H,m), 7.35-7.39(1H,m), 7.53-7.61 (3H,m), 8.03-8.08(1H,m)

Working Example 62

Pivaloyloxymethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 59%, m.p.: 130-135°C

Elemental Analysis for $C_{30}H_{31}N_7O_4.0.4CHCl_3.0.2H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	60.36;	5.30;	16.21
Found :	60.20;	5.20;	16.08

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.12(9H,s), 1.20(3H,t), 3.43(2H,q), 5.52(2H,s), 5.81(2H,s), 6.80(2H,d), 6.99(2H,d), 7.08(1H,t), 7.24(1H,dd), 7.43-7.68(5H,m)

Working Example 63

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

Yield: 76%, m.p.: 149-152° C

Elemental Analysis for $C_{33}H_{35}N_7O_5.0.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	64.06;	5.86;	15.85
Found :	64.27;	6.02;	15.86

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.12-1.88(16H,m), 3.38-3.47(2H,m), 4.48-4.59(1H,m), 5.51(2H,s), 6.75-6.88(5H,m), 7.04(1H,t), 7.29-7.40(2H,m), 7.47-7.51(3H,m), 7.91-7.95(1H,m)

Working Example 64

Methyl 2-allyloxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless crystals from methyl 2-allyloxy-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 28.
Yield: 30%, m.p.: 154-156° C.

Elemental Analysis for $C_{26}H_{22}N_6O_3.0.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	65.67;	4.88;	17.67
Found :	65.63;	4.71;	17.68

^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.75(3H,d), 4.58-4.61(1H,m), 4.92-4.95(1H,m), 5.18-5.48(2H,m), 5.52(2H,d), 5.83-6.15(1H,m), 6.98-7.05(2H,m), 7.09-7.17(2H,m), 7.35-7.44(2H,m), 7.47-7.60(3H,m), 8.09-8.19(1H,m)
IR(KBr) cm^{-1}: 1720, 1670, 1550, 1470, 1430, 1280, 1250, 1025, 760, 735

Working Example 65

Methyl 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless needles from methyl 2-butoxy-1-[(2'-cyanobiphenyl-4-yl)-methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 28.
Yield: 91%, m.p.: 146-148° C.

Elemental Analysis for $C_{27}H_{26}N_6O_3$:

	C(%)	H(%)	N(%)
Calcd.:	67.21;	5.43;	17.42
Found :	67.00;	5.45;	17.49

^{1}H-NMR(200MHz,$CDCl_3$) δ : 0.99(3H,t), 1.37-1.55(2H,m), 1.74-1.88(2H,m), 3.61(3H,s), 4.27(2H,t), 5.53(2H,s), 6.75(2H,d), 6.90(2H,d), 6.97(2H,d), 7.30-7.34(1H,m), 7.41 (2H,dd), 7.57-7.61(2H,m), 8.04-8.09(1H,m)
IR(KBr) cm^{-1}: 1720, 1600, 1540, 1470, 1430, 1270, 1250, 1020, 750

Working Example 66

Methyl 2-butylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless crystals from methyl 2-butylamino-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 41.
Yield: 42%, m.p.: 216-218° C.

Elemental Analysis for $C_{27}H_{27}N_7O_2.H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	64.91;	5.85;	19.63
Found :	64.86;	5.68;	19.41

^{1}H-NMR(200MHz,DMSO-d_6) δ : 0.91(3H,t), 1.25-1.43(2H,m), 1.52-1.67(2H,m), 3.65(3H,s), 5.47(2H,s), 6.79-(2H,d), 6.98-7.05(3H,m), 7.18(1H,dd), 7.42-7.64(5H,m)
IR(KBr) cm^{-1}: 1720, 1665, 1660, 1650, 1430, 1260, 745

Working Example 67

Methyl 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-morpholinobenzimidazole-7-carboxylate

The title compound was prepared as colorless crystals from methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-morpholinobenzimidazole-7-carboxylate according to the procedure for Working Example 41.
Yield: 62%, m.p.: 163-167° C.

Elemental Analysis for $C_{27}H_{25}N_7O_3.0.6CHCl_3$:

	C(%)	H(%)	N(%)
Calcd.:	58.45;	4.55;	17.29
Found :	58.66;	4.36;	17.54

^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.33(4H,t), 3.73(3H,s), 3.90(4H,t), 5.44(2H,s), 6.62(2H,d), 6.97(2H,d), 7.17(1H,t), 7.33-7.38(1H,m), 7.43-7.50(2H,m), 7.55-7.61(2H,m), 8.08-8.13(1H,m)
IR(KBr) cm^{-1}: 1730, 1600, 1530, 1455, 1420, 1405, 1280, 1260, 1120, 1110, 1000, 760, 750, 740

Working Example 68

Methyl 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-piperidinobenzimidazole-7-carboxylate

The title compound was prepared as colorless crystals from methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-piperidinobenzimidazole-7-carboxylate according to the procedure for Working Example 41.
Yield: 47%, m.p.: 146-150° C.

Elemental Analysis for $C_{28}H_{27}N_7O_2.0.8CHCl_3$:

	C(%)	H(%)	N(%)
Calcd.:	58.72;	4.76;	16.64
Found :	58.69;	4.66;	16.75

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.72(6H,brs), 3.11(4H,m), 3.61(3H,s), 5.38(2H,s), 6.45(2H,d), 6.80(2H,d), 6.89-6.96(2H,m), 7.28-7.37(2H,m), 7.56-7.64(2H,m), 8.01-8.06(1H,m)
IR(KBr) cm^{-1}: 1715, 1600, 1530, 1450, 1420, 1415, 1405, 1300, 1280, 1260, 1240, 1215, 1130, 770, 760, 750

Working Example 69

Methyl 2-ethylmethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless crystals from methyl 2-ethylmethylamino-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 41.
Yield: 54%, m.p.: 130-136° C (decomp.).

Elemental Analysis for $C_{26}H_{25}N_7O_2.0.6H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	59.26;	4.79;	18.19
Found :	59.04;	4.95;	18.05

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.19(3H,t), 2.57(3H,s), 3.22(2H,m), 3.62(3H,s), 5.40(2H,s), 6.43(2H,d), 6.78-6.94(4H,m), 7.30-7.34(1H,m), 7.57(1H,dd), 7.59-7.63(2H,m), 7.99-8.04(1H,m)
IR(KBr) cm^{-1}: 1720, 1600, 1540, 1435, 1400, 1300, 1280, 1255, 1015, 750, 740

Working Example 70

2-Piperidino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

The title compound was prepared as colorless crystals from methyl 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-piperidinobenzimidazole-7-carboxylate according to the procedure for Working Example 29.
Yield: 91%, m.p.: 215-218° C (decomp.).

Elemental Analysis for $C_{27}H_{25}N_7O_2.0.5CHCl_3$:

	C(%)	H(%)	N(%)
Calcd.:	61.25;	4.77;	18.18
Found :	60.95;	4.70;	17.90

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.65(6H,brs), 3.24(4H,brs), 5.48(2H,s), 6.71(2H,d), 6.92(2H,d), 7.17(1H,t), 7.42-7.48(2H,m), 7.54-7.67(2H,m)

IR(KBr) cm^{-1}: 1685, 1530, 1450, 1440, 1420, 1400, 1285, 1270, 1245, 750, 730

Working Example 71

2-Morpholino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

The title compound was prepared as colorless crystals from methyl 2-morpholino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 29.

Yield: 59%, m.p.: 202-206° C (decomp.).

Elemental Analysis for $C_{28}H_{23}N_7O_3.0.6CHCl_3$:

	C(%)	H(%)	N(%)
Calcd.:	57.76;	4.30;	17.73
Found :	57.55;	4.25;	17.66

^{1}H-NMR(200MHz,DMSO-d_6) δ : 3.24(4H,brs), 3.76(4H,brs), 5.56(2H,s), 6.72(2H,d), 6.93(2H,d), 7.16(1H,t), 7.41-7.70(6H,m)

IR(KBr) cm^{-1}: 1690, 1535, 1460, 1450, 1420, 1410, 1290, 1260, 1245, 1120, 760, 740

Working Example 72

2-(N-Ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

The title compound was prepared as colorless crystals from methyl 2-(N-ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 47.

Yield: 66%, m.p.: 204-206° C (decomp.).

Elemental Analysis for $C_{25}H_{23}N_7O_2.0.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	64.92;	5.23;	21.20
Found :	65.22;	5.31;	21.11

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.13(3H,t), 2.93(3H,s), 3.27(2H,m), 5.54(2H,s), 6.68(2H,d), 6.92(2H,d), 7.13(1H,t), 7.43-7.48(2H,m), 7.53-7.67(2H,m)

IR(KBr) cm^{-1}: 1725, 1620, 1550, 1540, 1460, 1440, 1420, 1300, 1250, 775

Working Example 73

2-Butylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

The title compound was prepared as colorless crystals from methyl 2-butylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 47.

Yield: 67%, m.p.: 213-216° C (decomp.).

Elemental Analysis for $C_{26}H_{25}N_7O_2.H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	64.32;	5.60;	20.19
Found :	64.07;	5.77;	20.16

^{1}H-NMR(200MHz,DMSO-d_6) δ : 0.89(3H,t), 1.22-1.41(2H,m), 1.51-1.66(2H,m), 3.34-3.43(2H,m), 5.65(2H,s), 6.83(2H,d), 6.97-7.05(3H,m), 7.29(1H,dd), 7.40-7.67(5H,m)
IR(KBr) cm^{-1}: 1660, 1580, 1540, 1485, 1440, 1380, 1340, 1215, 850, 810, 780, 760, 750

Working Example 74

2-Ethoxy-1-[(2'-carboxybiphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

To a solution of methyl 2-ethoxy-1-[(2'-methoxycarbonylbiphenyl-4-yl)methyl]benzimidazole-7-carboxylate (0.7 g) in methanol (10 ml) was added 1N NaOH (5 ml) and the mixture was stirred at 80° C for 3 hours. After evaporation of the methanol, the aqueous residue was neutralized with 1N hydrochloric acid to give crystals. The crystals were recrystallized from methanol - chloroform to afford colorless crystals (0.54 g, 83%), m.p. 213-215° C.

Elemental Analysis for $C_{24}H_{20}N_2O_5$:

	C(%)	H(%)	N(%)
Calcd.:	69.22;	4.84;	6.73
Found :	68.98;	4.89;	6.71

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.42(3H,t), 4.61(2H,q), 5.68(2H,s), 7.01(2H,d), 7.13-7.56(7H,m), 7.64-7.71-(2H,m)
IR(Neat)cm^{-1}: 1725, 1545, 1460, 1420, 1380, 1280, 1260, 1230, 1205, 1120, 1030, 750

Working Example 75

Methyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

The title compound was prepared as colorless crystals from methyl 2-ethylamino-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate according to the procedure for Working Example 41.
Yield: 63%, m.p.: 256-258° C.

Elemental Analysis for $C_{25}H_{23}N_7O_2.H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	63.68;	5.34;	20.79
Found :	63.99;	5.09;	20.68

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.21(3H,t), 3.40-3.60(2H,m), 3.63(3H,s), 5.47(2H,s), 6.78(2H,d), 6.98-7.05-(3H,m), 7.18(1H,dd), 7.42-7.66(5H,m)
IR(Neat)cm^{-1}: 1710, 1660, 1650, 1645, 1430, 1340, 1300, 1280, 1250, 1050, 740

Working Example 76

Methyl 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-(2,2.2-trifluoroethoxy)benzimidazole-7-carboxylate

The title compound was prepared as colorless needles (0.37 g, 77%) from methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-(2,2,2-trifluoroethoxy)benzimidazole-7-carboxylate (0.48 g) according to the procedure for Working Example 28.

m.p.: 210-212 °C.

Elemental Analysis for $C_{25}H_{19}F_3N_6O_3$:

	C(%)	H(%)	N(%)
Calcd.:	59.06;	3.77;	16.53
Found :	59.02;	3.71;	16.36

^{1}H-NMR(200MHz,$CDCl_3$) δ : 3.82(3H,s), 5.01(2H,q), 5.64(2H,s), 6.99(2H,d), 7.14(2H,d), 7.25(1H,t), 7.37-7.41-(1H,m), 7.51-7.63(3H,m), 7.71(1H,dd), 8.17-8.22(1H,m)

IR(KBr) cm^{-1}: 1710, 1550, 1425, 1275, 1240, 1180, 1160, 1055, 750

Working Example 77

1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)benzimidazole-7-carboxylic acid

The title compound was prepared as colorless crystals (0.23 g, 88%) from methyl 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)benzimidazole-7-carboxylate (0.27 g) according to the procedure for Working Example 47.

m.p.: 204-206 °C.

Elemental Analysis for $C_{24}H_{17}F_3N_6O_3.H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	57.26;	3.60;	16.69
Found :	57.09;	3.59;	16.72

^{1}H-NMR(200MHz,DMSO-d_6) δ : 5.28(2H,q), 5.66(2H,s), 6.98(4H,d), 7.23(1H,t), 7.44-7.68(5H,m), 7.72(1H,dd)

IR(KBr) cm^{-1}: 1690, 1540, 1470, 1430, 1270, 1225, 1210, 1160, 1050, 740

The following compounds as listed in Table 1 are prepared according to the procedures for Reference Examples and Working Examples disclosed herein.

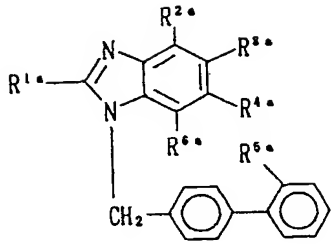


TABLE 1

Compound No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}
78	OEt	Me	H	H	Tet	COOH
79	OEt	OMe	H	H	Tet	COOH
80	OEt	NHMe	H	H	Tet	COOH
81	OEt	F	H	H	Tet	COOH
82	OEt	Cl	H	H	Tet	COOH
83	OEt	Br	H	H	Tet	COOH
84	OEt	CF_3	H	H	Tet	COOH
85	OEt	H	Me	H	Tet	COOH
86	OEt	H	OMe	H	Tet	COOH
87	OEt	H	NHMe	H	Tet	COOH
88	OEt	H	F	H	Tet	COOH
89	OEt	H	Cl	H	Tet	COOH
90	OEt	H	Br	H	Tet	COOH
91	OEt	H	CF_3	H	Tet	COOH
92	OEt	H	H	Me	Tet	COOH
93	OEt	H	H	OMe	Tet	COOH
94	OEt	H	H	NHMe	Tet	COOH
95	OEt	H	H	F	Tet	COOH
96	OEt	H	H	Cl	Tet	COOH
97	OEt	H	H	Br	Tet	COOH
98	OEt	H	H	CF_3	Tet	COOH
99	OEt	Me	H	H	COOH	COOH
100	OEt	H	Me	H	COOH	COOH
101	OEt	H	H	Me	COOH	COOH
102	OEt	H	H	H	COOH	COOH
103	OEt	Cl	H	H	COOH	COOH

TABLE 1 (continued)

Compound No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}
104	OEt	H	Cl	H	COOH	COOH
105	OEt	H	Cl	H	COOH	COOH
106	SEt	Me	H	H	Tet	COOH
107	NHMe	H	Me	H	Tet	COOH
108	OMe	H	H	Me	Tet	COOH
109	OPr	H	H	H	Tet	COOH
110	SMe	Me	H	H	Tet	COOH
111	OMe	H	H	H	Tet	Tet
112	OEt	H	H	H	Tet	Tet
113	OEt	Me	H	H	Tet	Tet
114	OEt	H			Tet	COOH
115	OEt			H	Tet	COOH
116	OEt	H	H	H	Tet	$COOCH_2OCO$-cyclo-Pr
117	OEt	H	H	H	Tet	$COOCH_2OCO$-sec-Bu
118	OEt	H	H	H	Tet	$COOCH_2OCO$-n-Bu
119	OEt	H	H	H	Tet	$COOCH_2OCO$-cyclo-Bu
120	OEt	H	H	H	Tet	$COOCH_2OCO$-n-Pen
121	OEt	H	H	H	Tet	$COOCH_2OCO$-i-Pen
122	OEt	H	H	H	Tet	$COOCH_2OCO$-sec-Pen
123	OEt	H	H	H	Tet	$COOCH_2OCO$-n-Hex
124	OEt	H	H	H	Tet	$COOCH_2OCO$-sec-Hex
125	OEt	H	H	H	Tet	$COOCH_2OCO$-n-Hep
126	OEt	H	H	H	Tet	$COOCH_2OCOCH_2Ph$
127	OEt	H	H	H	Tet	COOCH(Me)-OCOEt
128	OEt	H	H	H	Tet	COOCH(Me)-OCO-n-Pr
129	OEt	H	H	H	Tet	COOCH(Me)-OCO-i-Pr
130	OEt	H	H	H	Tet	COOCH(Me)-OCO-cyclo-Pr
131	OEt	H	H	H	Tet	COOCH(Me)-OCO-n-Bu
132	OEt	H	H	H	Tet	COOCH(Me)-OCO-i-Bu
133	OEt	H	H	H	Tet	COOCH(Me)-OCO-sec-Bu
134	OEt	H	H	H	Tet	COOCH(Me)-OCO-tert-Bu

TABLE 1 (continued)

Compound No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}
135	OEt	H	H	H	Tet	COOCH(Me)-OCO-cyclo-Bu
136	OEt	H	H	H	Tet	COOCH(Me)-OCO-n-Pen
137	OEt	H	H	H	Tet	COOCH(Me)-OCO-i-Pen
138	OEt	H	H	H	Tet	COOCH(Me)-OCO-sec-Pen
139	OEt	H	H	H	Tet	COOCH(Me)-OCO-cyclo-Pen
140	OEt	H	H	H	Tet	COOCH(Me)-OCO-n-Hex
141	OEt	H	H	H	Tet	COOCH(Me)-OCO-i-Hex
142	OEt	H	H	H	Tet	COOCH(Me)-OCO-sec-Hex
143	OEt	H	H	H	Tet	COOCH(Me)-OCO-cyclo-Hex
144	OEt	H	H	H	Tet	COOCH(Me)-OCO-n-Hep
145	OEt	H	H	H	Tet	COOCH(Et)-OCO-n-Pr
146	OEt	H	H	H	Tet	COOCH(Pr)-OCO-n-Bu
147	OEt	H	H	H	Tet	COOCH(iPr)-OCO-n-Pr
148	OEt	H	H	H	Tet	COOCH(Me)-OCO-OMe
149	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-n-Pr
150	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-i-Bu
151	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-sec-Bu
152	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-n-Pen
153	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-i-Pen
154	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-cyclo-Pen
155	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-n-Hex
156	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-cyclo-Hex
157	OEt	H	H	H	Tet	COOCH(Me)-OCO-O-cyclo-Hep
158	OMe	H	H	H	Tet	$COOCH_2OCO$-tert-Bu
159	OPr	H	H	H	Tet	$COOCH_2OCO$-tert-Bu
160	OMe	H	H	H	Tet	COOCH(Me)-OCO-O-cyclo-Hex
161	OPr	H	H	H	Tet	COOCH(Me)-OCO-O-cyclo-Hex
162	NHEt	H	H	H	Tet	$COOCH_2OCO$-tert-Bu
163	NHEt	H	H	H	Tet	$COOCH_2OCO$-O-cyclo-Hex

Experimental Example 1

Stable C-type crystalline 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate and preparation thereof

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate is usually purified by column chromatography on silica gel and the eluted fraction is concentrated to dryness to give amorphous powders. The powder is unstable by heat and impractical in production. For solving this problem, the present inventors made extensive experiments on crystallization of

the subject compound and discovered C-type crystalline form. The C-type crystal is unexpectedly stable by heat and quite useful for production. The C-type crystal of the title compound has approximately the following lattice spacings:

3.5 angstrom; middle
3.7 angstrom; weak
3.8 angstrom; middle
4.0 angstrom; middle
4.1 angstrom; weak
4.3 angstrom; weak
4.4 angstrom; middle
4.6 angstrom; middle
4.8 angstrom; middle
5.1 angstrom; middle
5.2 angstrom; weak
6.9 angstrom; weak
7.6 angstrom; weak
8.8 angstrom; middle
9.0 angstrom; strong
15.9 angstrom; weak

IR spectrum (KBr tablet) of the C-type crystal is shown in Figure 2 with the significant absorption maxima at 2942, 1754, 1717, 1615, 1549, 1476 and 750 cm^{-1} and its melting point is 158-166° C (decomposition). Representative X ray chart (powder method), IR spectra (KBr tablet) and differential scanning calorimeter patterns are shown in Figures 1-3, respectively.

The C-type crystal of 1-(cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate has advantages, for example;

1. It improves heat stability and practical utility.
2. Residual solvent can be minimized in crystals.
3. It can achieve industrial and clinical developments and give ecomomical benefits.

The concentrated residues, amorphous powders, and/or crystals except for the C-type crystal for obtaining the subject compound, are stirred in a suitable solvent to form the desired C-type crystal. In case where the C-type crystal is not formed, a small amount of the C-type crystal can be added as a seed to allow crystallization. Examples of such solvents are not limited to, as long as they afford the C-type crystal, but include lower alcohols (e.g. methanol, ethanol, isopropyl alcohol, etc.), a mixture of lower alcohol and water and a mixture of lower alkyl ketone (e.g. acetone, etc.) and water. Amounts of solvents used are not limited to, but practically, 2 to 30-fold per weight of the crystal. Ratios of lower alcohol vs. water and lower alkyl ketone vs. water are not limited to, but preferably 4:1 to 1:1. Stirring temperatures are not limited to, but -5° C to 40° C, preferably 0° C to 25° C.

Experimental Example 2

Inhibition of binding of angiotensin II to angiotensin receptor

[Method]

An experiment of inhibition on the binding of angiotensin II (A II) to A II receptor was conducted by modifying the method of Douglas et al. [Endocrinology, 102, 685-696 (1978)]. An A II receptor membrane fraction was prepared from bovine adrenal cortex.

The compound of the present invention (10^{-6}M or 10^{-7}M) and ^{125}I-angiotensin II (^{125}I-A II) (1.85 kBq/50 µl) were added to the receptor membrane fraction, and the mixture was incubated at room temperature for one hour. The receptor-bound and free ^{125}I-A II were separated through a filter (Whatman GF/B filter), and the radioactivity of ^{125}I-A II bound to the receptor was measured.

[Results]

The results relating to the compounds of the present invention are shown in Table 2.

Experimental Example 3

Inhibitory effect of the compound of the present invention on pressor action of A II

[Method]

Jcl : SD rats (9 week old, male) were employed. On the previous day of the experiment, these animals were applied with cannulation into the femoral artery and vein under anesthesia with pentobarbital Na. The animals were fasted but allowed to access freely to drinking water until the experiment was started. Just on the day of conducting the experiment, the artery cannula was connected with a blood-pressure transducer, and the average blood pressure was recorded by means of polygraph. Before administration of the drug, the pressor action due to intravenous administration of A II (100 ng/kg) as the control was measured. The drugs were orally administered, then, at each point of the measurement, A II was administered intravenously, and the pressor action was similarly measured. By comparing the pressor action before and after administration of the drug, the percent inhibition by the drug on A II-induced pressor action was evaluated.

[Results]

The results relating to the compounds of the present invention are shown in Table 2.

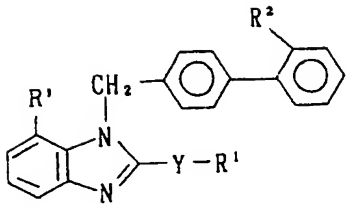
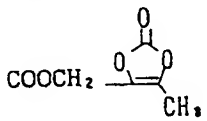
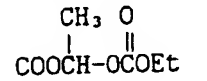
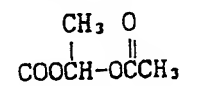
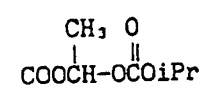
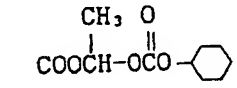


TABLE 2

Working Example No.	R¹	Y	R²	R'	Radioreceptor Assay 1x10 $^{-7}$M	1x10 $^{-6}$M	Pressor Response to AII (p.o.) 3mg/kg	
28	Et	O	Tet	COOEt	46	82	+++	a)
29	Et	O	Tet	COOH	61	91	+++	
30	Pr	O	Tet	COOEt	16	48	+++	
31	Pr	O	Tet	COOH	40	79	+++	
33	Me	S	Tet	COOEt	2	26	+	
34	Et	S	Tet	COOEt	17	54	+++	
35	Pr	S	Tet	COOEt	7	32	NT	
36	Me	S	Tet	COOH	51	82	+++	
37	Et	S	Tet	COOH	41	80	+++	
38	Pr	S	Tet	COOH	6	50	+++	
39	Et	O	Tet	COOMe	58	89	+++	
40	Et	NH	Tet	COOEt	54	83	+++	
41	Pr	NH	Tet	COOEt	45	57	NT	b)
43	Et	O	Tet	$COOCH_2OC(=O)tBu$	74	94	+++	
44	Et	O	Tet	$COOCH(CH_3)OC(=O)$-Ph	32	77	+++	
45	Me	O	Tet	COOMe	17	67	+++	
46	Me	O	Tet	COOH	66	88	+++	
47	Et	NH	Tet	COOH	84	96	+++	

TABLE 2 (continued)

Working Example No.	R¹	Y	R²	R'	Radioreceptor Assay 1x10 $^{-7}$M	1x10 $^{-6}$M	Pressor Response to A II (p.o.) 3mg/kg
48	Pr	NH	Tet	COOH	67	92	++
49	Et	O	Tet		66	91	+++
50	Et	O	Tet	$COOCH_2OCOCH_3$	63	92	+++
51	Et	O	Tet	$COOCH_2OCOEt$	44	84	+++
52	Et	O	Tet	$COOCH_2OCOPr$	48	84	+++
53	Et	O	Tet	$COOCH_2OCOiPr$	55	85	+++
54	Et	O	Tet		42	81	+++
55	Et	O	Tet		63	91	+++
56	Et	O	Tet		31	76	+++
57	Me	NH	Tet	COOH	41	79	NT
58	Et	O	Tet	$COOCH_2OCO$- 	55	84	+++
59	Et	O	Tet	$COOCH_2OCO$- 	37	69	+++
60	Et	O	Tet	COOCH=CH- 	44	81	+++
61	Et	O	Tet	$COOCH_2OCO$- 	54	89	+++
62	Et	NH	Tet	$COOCH_2OCOtBu$	48	87	+++
63	Et	NH	Tet		19	61	+++

a) +++ ≧ 70% > ++ ≧ 50% ≧ + > 30% > -

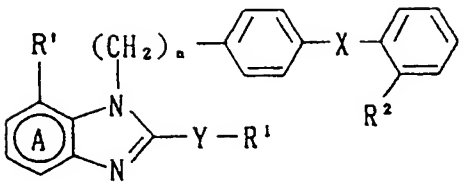
b) NT, not tested

It is understood that the preceding representative examples may be varied within the scope of the present invention by one skilled in the art to achieve essentially the same results.

As many widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that this invention is not limited to the specific embodiments thereof except as defined in the appended claims.

Claims

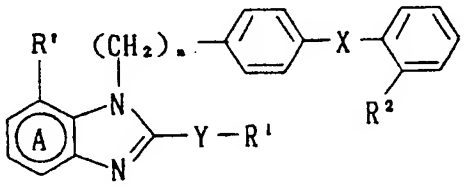
1. A compound of the formula:



(I)

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof, an amide thereof or a group capable of forming an anion or convertible to an anion; Y is -O-, $-S(O)_m-$ or $-N(R^4)-$ wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; or a pharmaceutically acceptable salt thereof.

2. A compound of according to claim 1, which is a compound of the formula:



(I")

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof or an amide thereof; Y is -O-, $S(O)_m-$ or $-N(R^4)-$wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein R^1 is an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or aralkyl group.

4. A compound according to claim 1, wherein R^1 is an alkyl, alkenyl, alkynyl, or cycloalkyl group, which may be substituted with hydroxyl, an optionally substituted amino group, halogen or a lower (C_{1-4}) alkoxy group.

5. A compound according to claim 1, wherein R^1 is a lower (C_{1-5}) alkyl or lower (C_{2-5}) alkenyl group optionally substituted with hydroxyl, an amino group, halogen or a lower (C_{1-4}) alkoxy group.

6. A compound according to claim 4, wherein the alkyl is a lower alkyl group having 1 to about 8 carbon atoms, which may be straight or branched.

7. A compound according to claim 6, wherein the lower alkyl group is unsubstituted or substituted with hydroxyl, an optionally substituted amino group, halogen or a lower (C_{1-4}) alkoxy group.

8. A compound according to claim 1, wherein R^1 is a lower alkyl group having 1 to about 8 carbon atoms.

9. A compound according to claim 3, wherein the aryl group is phenyl which may be substituted with halogen, nitro, lower (C_{1-4}) alkoxy, or lower (C_{1-4}) alkyl.

10. A compound according to claim 3, wherein the aralkyl group is phenyl-lower (C_{1-4}) alkyl which may be substituted with halogen, nitro, lower (C_{1-4}) alkoxy, or lower (C_{1-4}) alkyl.

11. A compound according to claim 1, wherein R^2 is carboxyl, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid, sulfonic acid, cyano, or lower (C_{1-4}) alkoxycarbonyl, which may be protected with an optionally substituted lower alkyl group or an acyl group.

12. A compound according to claim 1, wherein R^2 is a tetrazolyl group optionally protected with optionally substituted lower alkyl or acyl, a carboxyl group optionally protected with optionally substituted lower alkyl, or trifluoromethanesulfonic amide.

13. A compound according to claim 1, wherein R^2 is a tetrazolyl group.

14. A compound according to claim 1, wherein R' is a group having the formula: -CO-D' wherein D' is hydroxyl, optionally substituted amino or optionally substituted alkoxy.

15. A compound according to claim 1, wherein R' is a group having the formula: -CO-D' wherein D' is hydroxyl or optionally substituted alkoxy.

16. A compound according to claim 15, wherein D' is hydroxyl, a lower (C_{1-6}) alkoxy group optionally substituted with hydroxyl, optionally substituted amino, halogen, lower (C_{1-6}) alkoxy, lower (C_{1-6}) alkylthio or optionally substituted dioxolenyl on the alkyl moiety, or a group having the formula: -OCH-(R^7)OCOR^8 wherein R^7 is hydrogen, straight or branched lower alkyl having 1 to 6 carbon atoms, or cycloalkyl having 5 to 7 carbon atoms and R^8 is straight or branched lower alkyl having 1 to 6 carbon atoms, straight or branched lower alkenyl having 2 to about 8 carbon atoms, cycloalkyl having 5 to 7 carbon atoms, lower (C_{1-3}) alkyl which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms, lower (C_{2-3}) alkenyl which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms, optionally substituted aryl, straight or branched lower alkoxy having 1 to 6 carbon atoms, straight or branched lower alkenyloxy having 2 to about 8 carbon atoms, cycloalkyloxy having 5 to 7 carbon atoms, lower (C_{1-3}) alkoxy which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms, lower (C_{2-3}) alkenyloxy which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms, or optionally substituted aryloxy.

17. A compound according to claim 1, wherein R' is a group capable of forming an anion or convertible thereinto either chemically or under biological and/or physiological conditions.

18. A compound according to claim 1, wherein R' is a group capable of forming the residue: -COO- or convertible thereinto.

19. A compound according to claim 15, wherein D' is hydroxyl, a lower (C_{1-6}) alkoxy group optionally substituted with hydroxyl, lower (C_{1-6}) alkoxy or optionally substituted dioxolenyl on the alkyl moiety, a lower (C_{2-3}) alkenyloxy optionally substituted with optionally substituted aryl on the alkenyl moiety, or a group having the formula: -OCH(R^7)OCOR^8 wherein R^7 is hydrogen, or straight or branched lower alkyl having 1 to 6 carbon atoms and R^8 is straight or branched lower alkyl having 1 to 6 carbon atoms, cycloalkyl having 5 to 7 carbon atoms, lower (C_{1-3}) alkyl which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms, optionally substituted aryl, straight or branched lower alkoxy having 1 to 6 carbon atoms, cycloalkyloxy having 5 to 7 carbon atoms, lower (C_{1-3}) alkoxy which is substituted with optionally substituted aryl or cycloalkyl having 5 to 7 carbon atoms, or optionally substituted aryloxy.

20. A compound according to claim 1, wherein R' is carboxyl or a salt or anion thereof.

21. A compound according to claim 1, wherein R' is a group having the formula: -CO-OCH(R^7)OCOR^8 wherein R^7 is hydrogen or straight or branched lower alkyl having 1 to 6 carbon atoms and R^8 is straight or branched lower alkyl having 1 to 6 carbon atoms, cycloalkyl having 5 to 7 carbon atoms, optionally substituted phenyl, straight or branched lower alkoxy having 1 to 6 carbon atoms or cycloalkyloxy having 5 to 7 carbon atoms.

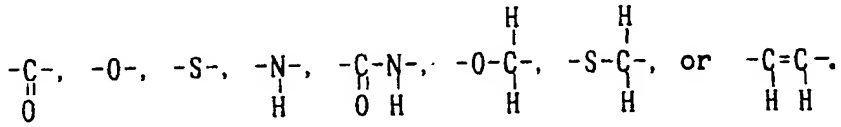
22. A compound according to claim 1, wherein R' is a tetrazolyl group optionally protected with optionally substituted lower alkyl or acyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid.

23. A compound according to claim 1, wherein the ring A is a benzene ring which may contain, in addition to the R' group, a substituent being selected from the group consisting of halogen nitro, cyano, optionally substituted amino, a group having the formula: -W-R^{13}
wherein W is a chemical bond, -O-, -S-, or

and R^{13} is hydrogen or an optionally substituted lower alkyl group, a group having the formula: -$(CH_2)_p$-CO-D wherein D is hydrogen, hydroxyl, optionally substituted amino, or optionally substituted alkoxy, and p is 0 or 1, tetrazolyl optionally protected with an optionally substituted lower alkyl group or an acyl group, trifluoromethanesulfonic amide, phosphoric acid, or sulfonic acid.

24. A compound according to claim 1, wherein the ring A is a benzene ring which contains no substitution in addition to the R' group.

25. A compound according to claim 1, wherein X is a chemical bond, lower (C_{1-4}) alkylene,

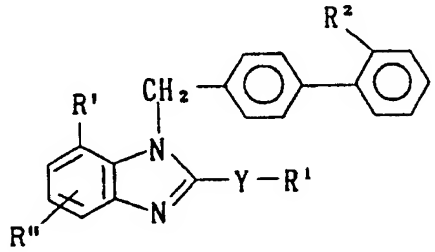


26. A compound according to claim 1, wherein X is a chemical bond between the phenylene group and the the phenyl group.

27. A compound according to claim 1, wherein Y is -O-, -SO_m- wherein m is 0, 1, or 2, or -N(R^4)- wherein R^4 is hydrogen or an optionally substituted lower (C_{1-4}) alkyl group.

28. A compound according to claim 1, wherein Y-R^1 is -N(R^4)-R^1 wherein R^1 and R^4 are taken together with the N atom attached thereto to form a heterocyclic ring.

29. A compound according to claim 1, which is a compound of the formula (I'):



(I')

wherein R^1 is lower (C_{1-5}) alkyl optionally substituted with hydroxyl, amino, halogen, or a lower (C_{1-4}) alkoxy group; R' is -CO-D' wherein D' is hydroxyl, amino, N-lower (C_{1-4}) alkylamino, N,N-dilower (C_{1-4}) alkyl amino, or lower (C_{1-4}) alkoxy optionally substituted with hydroxyl, amino, halogen, lower (C_{1-4}) alkoxy, lower (C_{2-6}) alkanoyloxy or 1-lower (C_{1-6}) alkoxycarbonyloxy on the alkyl moiety, or tetrazolyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl or acyl group; R^2 is tetrazolyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl or acyl group, or carboxyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl group; R'' is hydrogen, halogen, lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy, nitro or -CO-D'' wherein D'' is hydroxyl or lower (C_{1-2}) alkoxy optionally substituted with hydroxyl, lower (C_{1-4}) alkoxy, lower (C_{2-6}) alkanoyloxy or 1-lower

(C_{1-6}) alkoxycarbonyloxy on the alkyl moiety, or amino optionally substituted with lower (C_{1-4}) alkyl; Y is -O-, -S-, or -N(R^4)- wherein R^4 is hydrogen or an lower (C_{1-4}) alkyl group; or a pharmaceutically acceptable salt thereof.

30. A compound according to claim 29, which R^1 is lower (C_{1-5}) alkyl.

31. A compound according to claim 29, which R' is -CO-D' wherein D' is hydroxyl, or lower (C_{1-4}) alkoxy optionally substituted with hydroxyl, lower (C_{1-4}) alkoxy, lower (C_{2-6}) alkanoyloxy or 1-lower (C_{1-6}) alkoxycarbonyloxy on the alkyl moiety, or tetrazolyl optionally protected with an optionally substituted lower (C_{1-4}) alkyl or lower (C_{2-5}) alkanoyl.

32. A compound according to claim 29, which R^2 is tetrazolyl optionally protected with lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy lower (C_{1-4}) alkyl, triphenylmethyl, p-methoxybenzyl, p-nitrobenzyl, lower (C_{2-5}) alkanoyl or benzoyl, or carboxyl optionally protected with lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy lower (C_{1-4}) alkyl, triphenylmethyl, p-methoxybenzyl or p-nitrobenzyl.

33. A compound according to claim 29, which R'' is hydrogen, lower (C_{1-4}) alkyl, or halogen.

34. A compound according to claim 29, which R'' is hydrogen.

35. A compound according to claim 29, which Y is -O-.

36. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is 2-ethoxy-1-[-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid or a pro-drug thereof.

37. A compound according to claim 1, which is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.

38. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of
ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
ethyl 2-propoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
p-propoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
ethyl 2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
ethyl 2-ethylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
ethyl 2-propylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
2-ethylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
2-propylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
methyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
ethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-carboxylate,
ethyl 2-propylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
pivaloyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]benzimidazole-7-carboxylate,
methyl 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
2-methoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
2-propylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid,
(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate,
acetoxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
propionyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate,
butyryloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
isobutyryloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
1-(ethoxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
1-acetoxyethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
1-(isopropoxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5- yl)biphenyl-4-yl]methyl]benzimidazole-7-

carboxylate,
cyclohexylcarbonyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
benzoyloxymethyl 2-ethoxy-1-[[2'-1H-tetrazol-5-yl)biphenyl-4- yl]methyl]benzimidazole-7-carboxylate,
(E)-cinnamoyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
cyclopentylcarbonyloxymethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate,
pivaloyloxymethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate, and
1-(cyclohexyloxycarbonyloxy)ethyl 2-ethylamino-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate.

39. A stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate.

40. A stable crystal according to claim 39, which has approximately the following lattice spacings:
3.5 angstrom; middle
3.7 angstrom; weak
3.8 angstrom; middle
4.0 angstrom; middle
4.1 angstrom; weak
4.3 angstrom; weak
4.4 angstrom; middle
4.6 angstrom; middle
4.8 angstrom; middle
5.1 angstrom; middle
5.2 angstrom; weak
6.9 angstrom; weak
7.6 angstrom; weak
8.8 angstrom; middle
9.0 angstrom; strong
15.9 angstrom; weak.

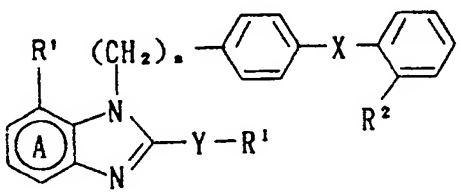
41. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a compound according to one of claims 1 - 38 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutical acceptable carrier, excipient or diluent.

42. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a crystal according to claim 39 or 40 in admixture with a pharmaceutical acceptable carrier, excipient or diluent.

43. A use of a compound according to one of claims 1-38 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

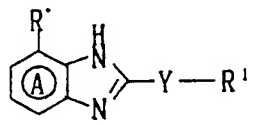
44. A use of a crystal according to claim 39 or 40 for the manufacture of a medicament for antagonizing angiotensin II.

45. A method for producing a compound of the formula (I):



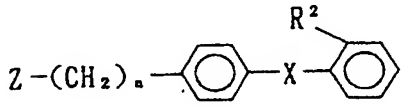
(I)

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof, an amide thereof or a group capable of forming an anion or convertible to an anion; Y is -O-, $S-(O)_m$ - or $-N(R^4)-$ wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; or a pharmaceutically acceptable salt thereof, which comprises (i) reacting a compound of the formula (II):



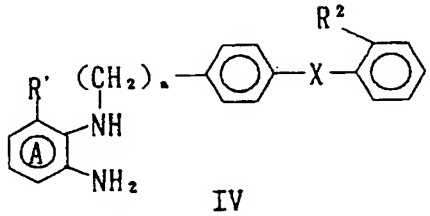
II

wherein R^1, R', A and Y have the above-defined meanings, with a compound of the formula (III):



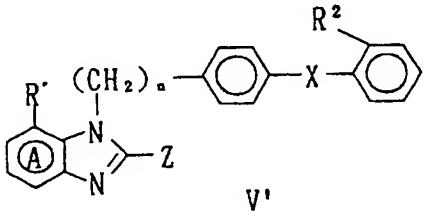
III

wherein R^2, X and n have the above-defined meanings and Z is halogen, (ii) reacting a compound of the formula (IV):



IV

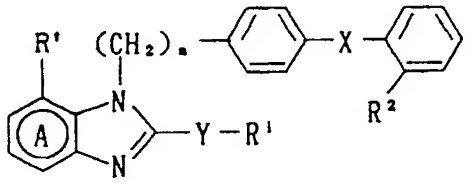
wherein each group has the above-defined meaning, with alkyl orthocarbonate, a carbonylating or thiocarbonylating reagent, or isothiocyanate, (iii) reacting a compound of the formula (V'):



V'

wherein each group has the above-defined meaning, with a nucleophilic reagent,
and, if desired, converting a product obtained by the above processes (i) to (iii) into a compound of the formula (I) by azidation, hydrolysis, reduction, halogenation, O-, N- or S-alkylation, nucleophilic reaction, ring closure, acylation, esterification, oxidation and/or deprotection, and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

46. A method according to Claim 45, wherein said compound is a compound of the formula:



(I")

wherein the ring A is a benzene ring which may optionally contain substitution in addition to the R' group; R^1 is hydrogen or an optionally substituted hydrocarbon residue; R^2 is a group capable of forming an anion or a group convertible thereinto; X is a direct bond or a spacer having an atomic length of two or less between the phenylene group and the phenyl group; R' is carboxyl, an ester thereof or an amide thereof; Y is -O-, $-S(O)_m$ - or $-N(R^4)$-wherein m is an integer of 0, 1 or 2 and R^4 is hydrogen or an optionally substituted alkyl group; and n is an integer of 1 or 2; or a pharmaceutically acceptable salt thereof.

47. A method according to Claim 45, wherein said compound is 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid, or a pharmaceutically acceptable salt or pro-drug thereof.

48. A method according to Claim 45, wherein said compound is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.

49. A method according to Claim 45, which gives a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate, which has approximately the following lattice spacings:
3.5 angstrom; middle
3.7 angstrom; weak
3.8 angstrom; middle
4.0 angstrom; middle
4.1 angstrom; weak
4.3 angstrom; weak
4.4 angstrom; middle
4.6 angstrom; middle
4.8 angstrom; middle
5.1 angstrom; middle
5.2 angstrom; weak
6.9 angstrom; weak
7.6 angstrom; weak
8.8 angstrom; middle
9.0 angstrom; strong
15.9 angstrom; weak.

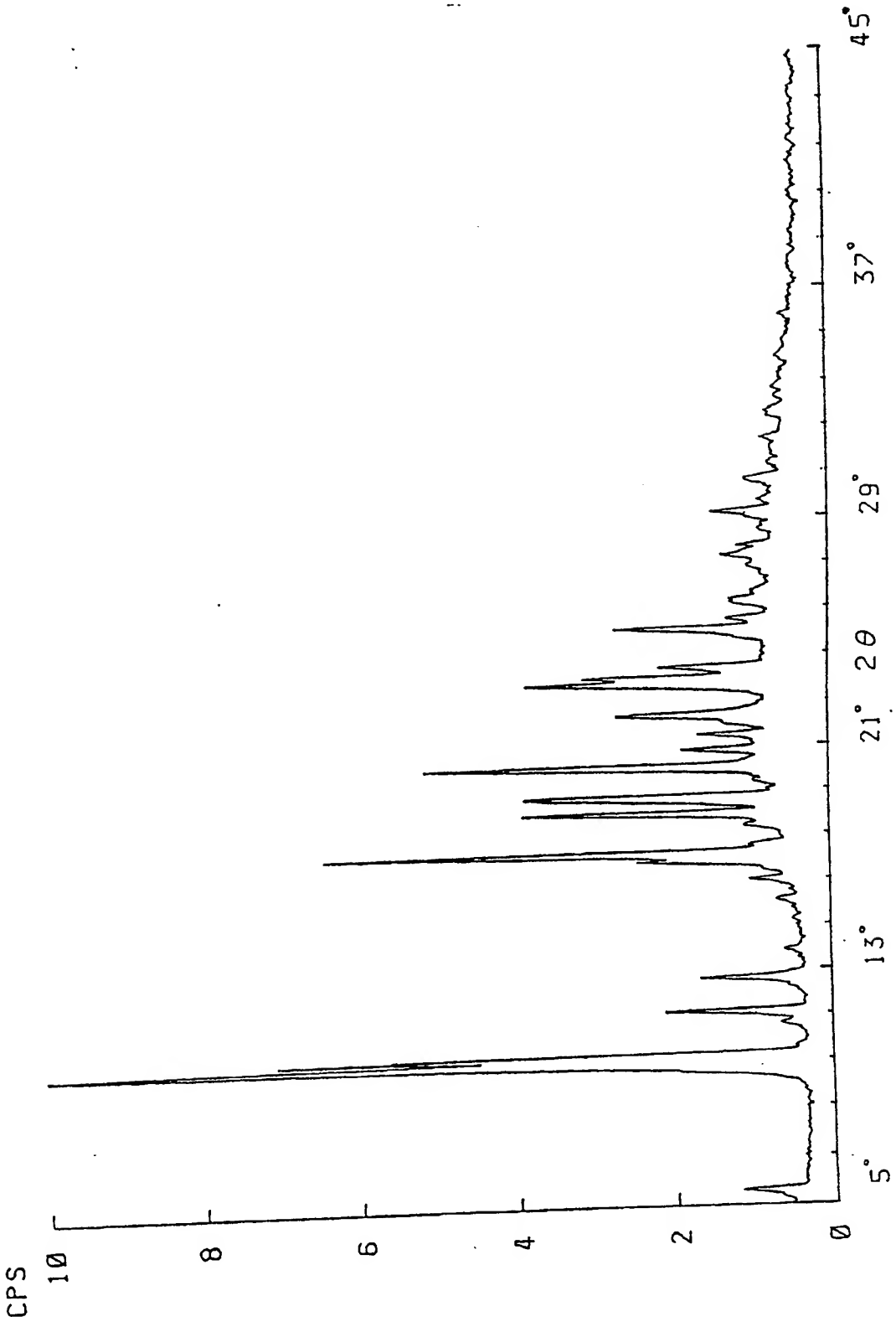


Figure 1

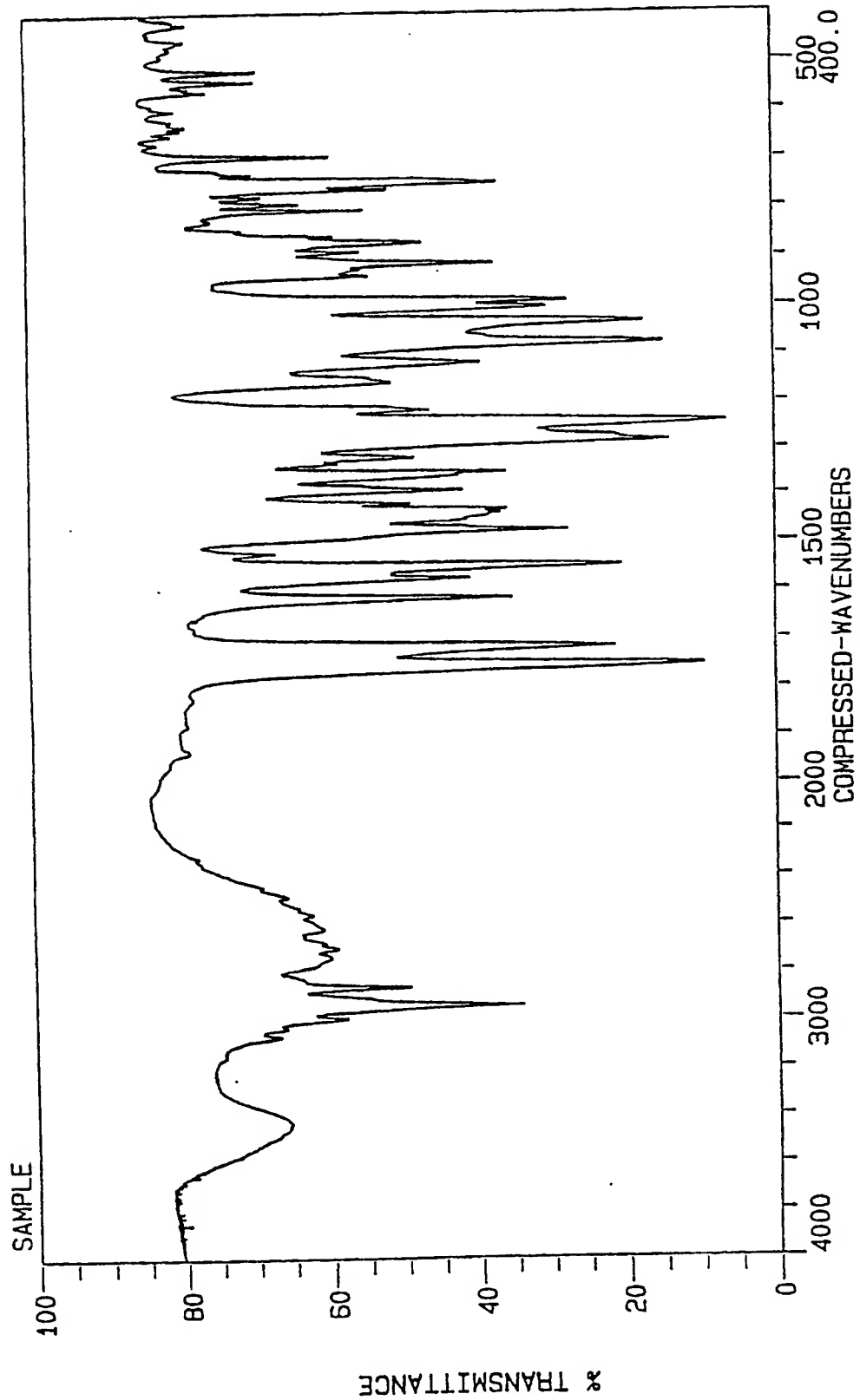

SAMPLE
100
80
60
40
20
0
% TRANSMITTANCE
4000
3000
2000
1500
1000
500
400.0
COMPRESSED-WAVENUMBERS

Figure 2

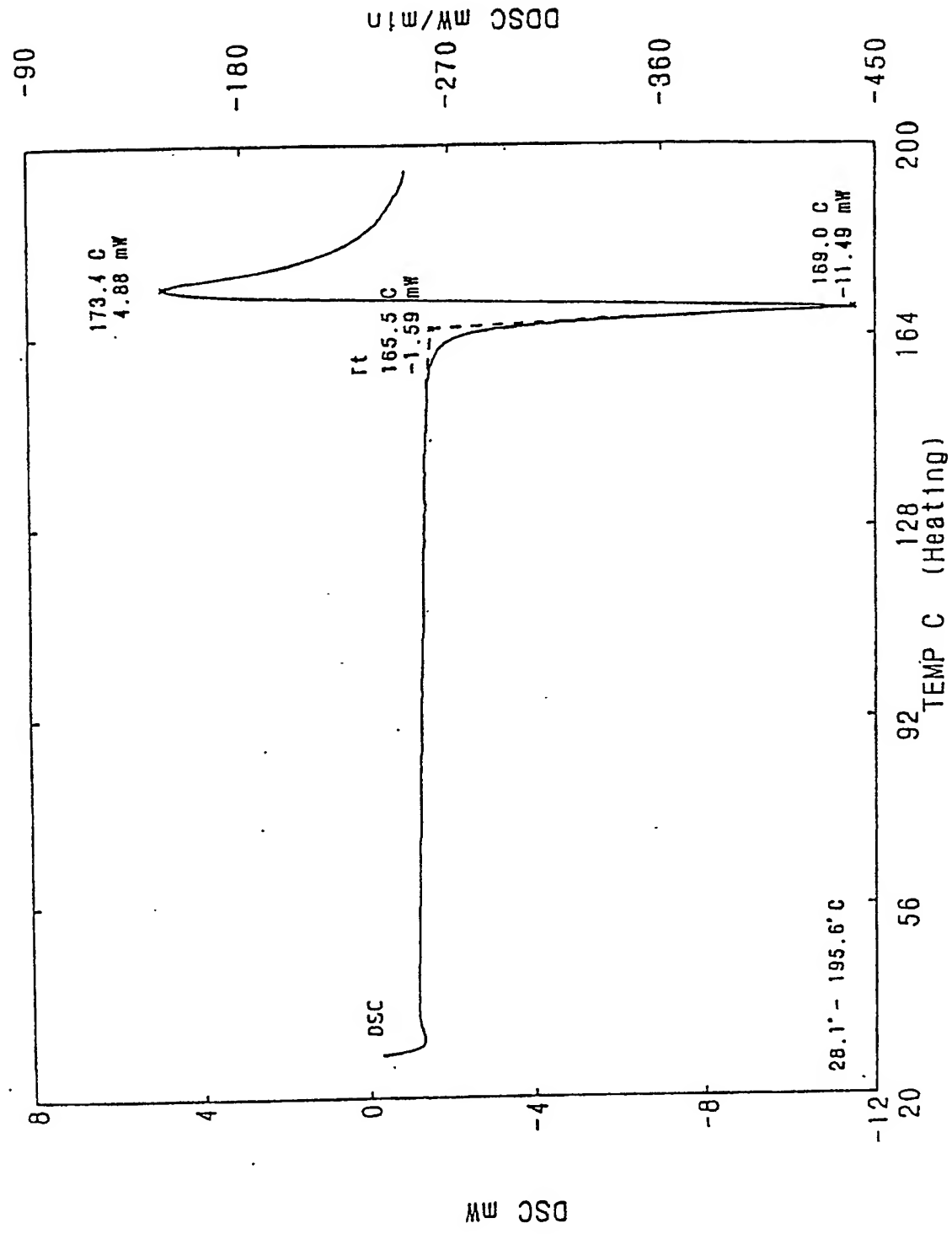

DSC mW/min
-90
-180
-270
-360
-450
173.4 C
4.88 mW
169.0 C
-11.49 mW
rt
165.5 C
-1.59 mW
DSC
28.1°- 195.6°C
8
4
0
-4
-8
-12
20
56
92
128
164
200
TEMP C (Heating)
DSC mW

Figure 3

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number

EP 91 10 6330

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,X	EP-A-0 400 835 (MERCK & CO, INC) * The whole document *	1-38,41-43,45-48	C 07 D 235/26 A 61 K 31/415 C 07 D 235/28 C 07 D 235/30 C 07 D 235/02 C 07 D 403/10 A 61 K 31/41
P,X	EP-A-0 420 237 (EISAI CO., LTD) * The whole document *	1-14,16-17,23-38,41-43,45-48	
P,A	EP-A-0 392 317 (DR. KARL THOMAE)		
P,A	EP-A-0 399 732 (IMPERIAL CHEMICAL IND.)		

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 235/00
A 61 K 31/00
C 07 D 403/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

As the drafting of the claims is not clear and concise(Art. 83-84 EPO) and encompasses such an enormous amount of products, a complete search is not possible on economic grounds(see Guidelines for Examination in the EPO, Part B, Chapter III, 2.) So the search has been based (Rule 4.5) on the examples.

Place of search	Date of completion of the search	Examiner
THE HAGUE	04-08-1991	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03 82 (P0407)

脳血管障害の発症・再発とその予防

——久山町研究より

藤島正敏
九州大学医学部第二内科学教室

● Masatoshi FUJISHIMA
Primary and secondary prevention for cerebrovascular disease from the Hisayama study

◉脳卒中の発症はその危険因子，とくに高血圧の適切な治療で予防できる．しかし，糖尿病のリスクが近年増えている．一方，再発は降圧治療のみでは予防できない．

キーワード：脳卒中，脳梗塞，危険因子，高血圧，降圧治療

脳血管疾患の死亡率は，死亡診断書の書式が改正された1995年以降，わが国の死因別死亡の第二位に再浮上した．アメリカにおいても，脳卒中の死亡率は1992年の26.2/10万人を底値として，以後増加に転じている．

脳血管障害はその分類（「サイドメモ」参照）にも示すように多くの病型があり，そのリスクファクターは病型によって異なる．脳血管障害の発症予防を論じる場合には，危険因子を抜きには考えられない．

本稿では，脳血管障害のすべてを取り上げることはできないので，脳卒中の代表的な病型である脳梗塞と脳出血に限って予防を考えてみよう．脳出血の90%以上は高血圧性であり，高血圧が最大のリスクである．一方，脳梗塞は臨床病型によりリスクは異なり，ラクナ梗塞は高血圧，アテローム血栓性脳梗塞は糖尿病，高血圧，高脂血症，心原性脳塞栓症は心房細動が主要なリスクである．つまり，これらのリスクを早期発見し，適切な管理治療をすることが脳卒中の一次（発症）予防につながる．

■一般住民における脳卒中の実態

——久山町研究

久山町研究（40歳以上の住民を対象にした心血管病の前向き悉皆調査，剖検率82%）から得られ

サイドメモ　脳血管障害の病型分類と危険因子

脳血管障害の分類は，アメリカの分類III版（NINDS，1990年）がわが国でも広く用いられている（下の図参照）．

脳血管障害の危険因子は，管理可能な因子として高血圧，糖尿病，高脂血症，肥満，心疾患，不整脈，血液疾患などの各疾患と，飲酒，喫煙，ストレスなどライフスタイルに関連した因子がある．一方，管理不可能な因子として年齢，性，人種，気候，遺伝などがあげられる．脳血管障害の危険因子はけっして固定したものではなく，時代とともにそのリスクは変わる．

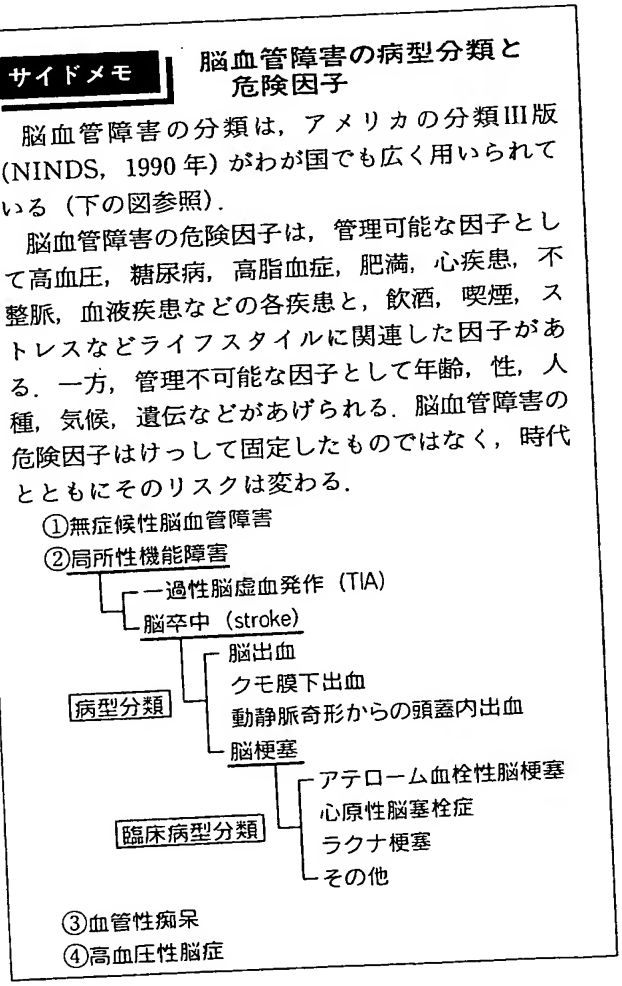


表 1　脳卒中病型別の[redacted]率・発症率の時代的変化（久山町 3 集団，40 歳[redacted]上，追跡各 8 年，性・年齢調整）

脳卒中	病　型	第 1 集団 (1961～1969 年)	第 2 集団 (1974～1982 年)	第 3 集団 (1988～1996 年)
死亡率 (対 1,000 人/年)	全脳卒中	4.8	1.6*	1.1*
	脳梗塞	1.8	0.8*	0.5*
	脳出血	2.0	0.5*	0.2*+
	クモ膜下出血	0.6	0.2	0.4
発症率 (対 1,000 人/年)	全脳卒中	10.5	5.0*	4.7*
	脳梗塞	7.0	3.7*	3.1*
	脳出血	2.3	0.8*	1.0*
	クモ膜下出血	0.9	0.5	0.7

*：$p<0.05$ vs. 第 1 集団，+：$p<0.05$ vs. 第 2 集団.

表 2　高血圧および降圧薬服用の頻度と血圧平均値の時代的推移（久山町 3 集団の断面調査，40 歳以上，年齢調整）

調査	高血圧の頻度 高血圧者/全対象者（%）		降圧薬服用の頻度 服用者/高血圧者（%）		高血圧者の血圧平均値 (収縮期/拡張期) (mmHg)	
	男性	女性	男性	女性	男性	女性
1961 年	28	24	10	11	175 /96	179 /94
1974 年	24*	24	37	35	167* /91*	173* /89*
1988 年	23*	21	62	70	157*+/87*+	161*+/82*+

高血圧：血圧≧160/95 mmHg または降圧薬服用.
*：$p<0.05$（vs. 1961 年）；+：$p<0.05$（vs. 1974 年）

た脳卒中の実態と時代的推移を紹介しよう[1]. 1961，1974，1988 年に設定した 3 集団における追跡各 8 年間の脳卒中死亡率，発症率を表 1 に示す. 全脳卒中死亡率は，第 2 集団（1974 年）で第 1 集団（1961 年）の 1/3 に著減，第 3 集団（1988 年）でもさらに減少したが，第 2 集団との間には有意差はない. 病型別では脳出血の減少は著しく，第 2 集団で 1/4，第 3 集団では 1/10 へとさらに有意に減少した.

一方，全脳卒中の発症率は第 2 集団で 1/2 に減少したが，第 3 集団では横ばいとなる. 病型別では，脳出血が第 2 集団で 1/3 に著減したものの，第 3 集団ではやや増加傾向にある. 脳梗塞も第 2 集団で約 1/2 に減少したが，第 3 集団では減少率が頭打ちとなる. 以上のように，脳卒中は 1960 年代に比べて 1970～1980 年代前半には著減（死亡，発症）したものの，1980 年代後半～1990 年代には減少率は鈍化したといえる.

■高血圧の頻度と降圧治療

脳卒中発症率の低下は高血圧の管理治療によると容易に考えられる. 久山町 3 集団における高血圧の頻度，治療率，血圧値を表 2 に示す. 高血圧（≧160/95 mmHg または降圧薬服用者）の頻度は，1961 年は全対象者（40 歳以上）の 28%（男性），24%（女性）であったのに対して，1988 年には男性は減少（5%減），女性は不変（3%減）で，高血圧の頻度そのものは時代的変化が小さい. 降圧薬服用率は 1961 年では高血圧者の 10～11%にすぎず，1974 年には約 1/3，1988 年には約 2/3 と，年々その比率は高くなった.

治療率の上昇によって，高血圧者の血圧値の平均はこの間に有意に低下した. 第 1 集団の血圧値（収縮期/拡張期）に比べて，第 2 集団の男性では平均 8/5 mmHg 低下，さらに第 3 集団では 18/9 mmHg 低下，同様に女性では 6/5，18/12 mmHg 低下した. その結果，1988 年は男女ともに高血圧といえども拡張期血圧の平均値は 90 mmHg を割っている. つまり，高血圧の管理治療によって血圧レベルは低下し，これが脳卒中の発症を抑えた（予防）と考えられる. なお，脳出血の発症・

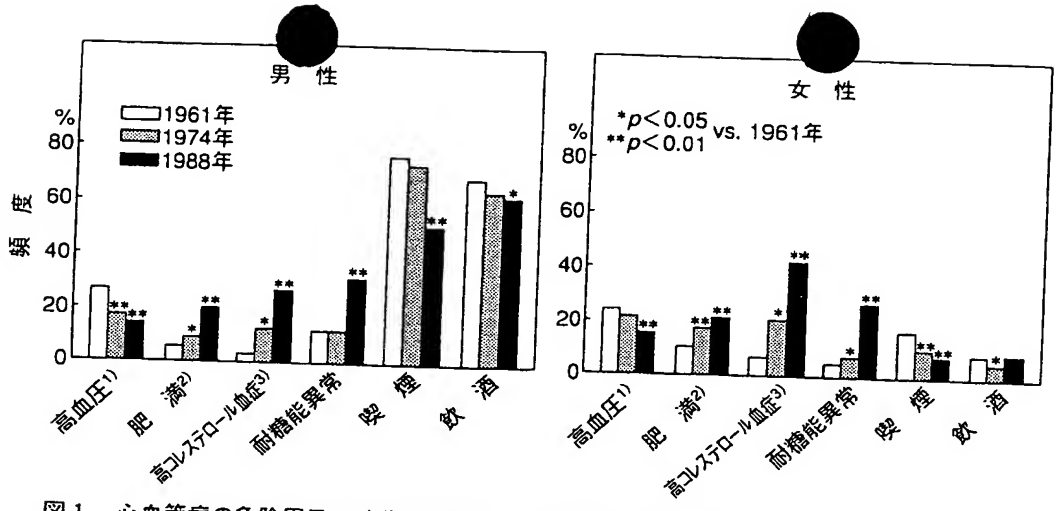


図1　心血管病の危険因子の時代的推移（久山町断面調査の比較，40歳以上，年齢調査）
1)BP≧160/95 mmHg，2)BMI≧25.4 kg/m²，3)≧220 mg/dl

表3　脳梗塞の危険因子の相対危険
（久山町，40歳以上，第1集団32年追跡および第3集団8年追跡）

危険因子	第1集団（1961～1993年）		第3集団（1988～1996年）	
	男性	女性	男性	女性
年齢*	2.4	2.6	3.7	2.4
収縮期血圧*	1.4	1.6		
耐糖能異常，HbA1c		1.9		1.5
心電図異常	1.8			
動脈硬化指数*			1.4	
body mass index*				
飲酒				

Cox比例ハザードモデル・逐次変数選択法，有意水準：$p<0.05$.
*：1標準偏差上昇のリスク，心電図異常：左室肥大またはST低下.

死亡の著しい減少は，降圧治療とともに栄養状態の改善による影響も無視できない.

■危険因子の時代的変化

高血圧の頻度，重症度はこの30年間に低下したものの，その一方で生活様式，とくに食生活の欧米化によって肥満，高脂血症，耐糖能異常がこの間に増えつづけている（図1）[2]．なかでも，糖尿病は1988年の調査では40歳以上の10%（WHO基準），耐糖能障害（IGT）が約20%に認められ[3]，この頻度は全国でほぼ一致している．近年，糖尿病は高血圧に匹敵するほどの脳梗塞の重要なリスクになっている．久山町第3集団の追跡調査（1988～1996年）では，正常血糖群に比べて糖尿病群の脳梗塞発症率は男性で3.5倍，女性で2倍と有意に高い.

高コレステロール血症（総コレステロール：C≧220 mg/dl）の頻度は，1961年と1988年では男性で9倍，女性で6倍増えたが，高C血症自体は脳卒中のリスクにはならない．しかし，動脈硬化指数（総C-HDL・C）/HDL・Cでは，低値群（≦2.6）に比べて高値群（>3.6）の脳梗塞発症率は男性においてのみ3.5倍の高値を示す．なお，低HDL・C血症（<45 mg/dl）は単独で脳梗塞のリスクになる.

男性の60%は飲酒者，50%は喫煙者である（1988年）．1.5合/日以上の飲酒は，脳出血，脳梗塞の発症率を有意に上昇させ，一方喫煙は，脳梗塞，なかでもラクナ梗塞の発症率を有意にあげ

る[4]．

■リスクファクターの是正と発症予防

脳卒中の発症率が第2集団で低下したものの，第3集団でその低下率が鈍化した理由は，高血圧治療により脳卒中発症の予防が代謝異常の増加により相殺されたとも考えられる．脳卒中の一次予防は，高血圧の管理治療のみでは防ぐことはできない．その他のリスクファクターの是正は不可欠であり，とくに，近年増えつづけている糖尿病管理の重要性を強調したい．

危険因子の相対危険は，病型，時代によって変わりうる．脳梗塞を例にとると（表3），久山町第1集団（1961～1993年，32年間追跡）と第3集団（1988～1996年，8年間追跡）では，年齢は男女を問わず有意な独立した危険因子であり，近年その傾向が一段と強い．一方，血圧は第3集団ではもはや有意な因子ではない．しかし，これは高血圧治療を否定するものではない．高血圧の管理が普及したために有意さが失われたにすぎず，逆に降圧治療こそが脳梗塞の発症予防につながることを示唆している．その他の危険因子である糖尿病，高脂血症，不整脈などが今後その危険度を増してくると考えられる．

脳卒中は，病型のいかんを問わず高齢化の傾向がいっそう顕著になってきた．さらに，病型もかつての日本人の特徴とされたラクナ梗塞（全脳梗塞の50%以上）や脳出血（全脳卒中の20%）が減り[5]，欧米型のアテローム血栓性脳梗塞や心原性脳塞栓症が相対的に増えている[1]．とくに，70歳代をピークに脳梗塞の1/3を占める脳塞栓症は，加齢とともに有病率が増える非弁膜性心房細動がその原因疾患でもあり，高齢者の脳梗塞の発症予防は，降圧治療とともに心房細動への対応が重要である．

■脳卒中再発の危険因子

脳卒中再発の危険因子は発症の危険因子と基本的に変わらない．他病型の再発をきたすこともあるが，通常は脳出血は出血を，脳梗塞は梗塞を再発することが多い．とくに，心原性脳塞栓症は再発しやすく，心房細動とそれに伴う心室内血栓形成が再発要因である．

しかし，再発リスクとしての高血圧の関与はさまざまで，その危険性も報告によって異なる．脳梗塞発症後2年間の累積再発率14.1%のStroke Data Bank（1991年）の調査[5]でも，脳卒中再発の危険因子のなかで拡張期高血圧（≧100 mmHg）の相対危険は1.01（95%CI：1.00～1.02）と小さく，むしろ糖尿病は1.66（1.14～2.42）と高い．脳卒中既発症の高血圧において，降圧治療が再発を予防するかどうかについては賛否両論があり，意見の一致をみていない．しかし，これまでの報告は後向き調査で規模も大小さまざまであり，結論が導き出せなかったともいえる．一方，メタアナリシス（9試験，計6,752名）によれば[6]，治療群の致死・非致死的脳卒中の再発率は対照群に比べて有意に低い．その相対危険は0.75（95%CI：0.61～0.85）であり，重篤かつ不利益な作用もみられていない．しかし，これらの効果が降圧治療によるものか，薬剤そのものの効果かの断定はできず，正常血圧でハイリスクの脳卒中患者との比較をしなくてはならない．

現在，世界的な規模で多施設多数例を対象に，ACE阻害薬を実薬とした再発予防効果の前向き調査（PROGRESS，1996年）が開始されたばかりである．この結果を得るにはあと数年を要する．再発の危険因子は，多少の議論はあるものの，高血圧は重要である．ほかには，加齢，糖尿病，高脂血症，心疾患（心筋梗塞，不整脈），血液性状異常などもリスクである．ややもすると降圧治療のみに注意が向けられがちであるが，抗血小板療法，抗凝血療法，抗不整脈治療，循環改善療法など，他のリスクの治療が適切に行われなくてはならない．

■脳卒中合併例の降圧治療

脳卒中を伴う高血圧は，糖尿病，高脂血症，肥満を合併し，かつ心臓，腎，末梢動脈の血管病変を高率に伴っている．このような状態では，降圧治療がかならずしも脳卒中の再発を予防しないことは容易に考えられる．つまり，①脳梗塞既発症では脳動脈の硬化性変化も進行し，降圧治療によっても血管病変の改善が期待できない，②主幹動脈の狭窄・閉塞を伴うアテローム血栓性脳梗塞は血行力学的機序によっても起こるので，降圧が逆に脳虚血を引き起こす，③心原性脳塞栓症は高

血圧の直接関与がないなどがそ[redacted]由である．

さらに，慢性期脳卒中患者の脳循環動態は非脳卒中患者とかなり異なる[7]．①病巣（梗塞，出血）は限局性でも脳血流は広範囲に低下し，②脳血流自動調節の下限域は上方へ偏位している．このことはわずかな血圧下降でも脳血流がさらに低下し，脳虚血に陥る．脳梗塞再発と血圧レベルとの間にJカーブ現象があるとの報告[8]もあり，さらに，夜間の血圧下降と再発との関連性も指摘されるなど，降圧治療がかならずしも脳循環動態を改善しないことが再発を予防できない一因とも考えられる．

■降圧治療の実際と注意点

そこで，降圧治療を行うにあたっては，①脳卒中発症後1カ月をすぎた（慢性期）時点においても高血圧が持続する場合に降圧治療を開始する，②降圧目標レベル（一次目標）は150～170/95 mmHg以下，または収縮期血圧は年齢＋100 mmHg以下と年齢を考慮し，③最低2カ月をかけて緩徐に行う，④脳出血は脳梗塞より5～10 mmHg低めとし，拡張期血圧は90 mmHg以上に再出血例が多い[9]ことから90 mmHg以下にする．一方，主幹動脈の狭窄・閉塞例はやや高めにとどめる，⑤長期降圧治療を行うと一次目標レベルをさらに下廻り，正常血圧に達することもあるが，脳循環不全症状（目まい，立ちくらみ，頭重感，気力・意欲の低下など）あるいは他臓器の循環障害（心筋虚血，腎不全，末梢動脈閉塞）の出現をみないかぎり，その血圧レベルを維持する．⑥降圧薬は，脳血管，脳循環への作用を考え[10]，Ca拮抗薬（持効型）を第一選択薬とし，ACE阻害薬を併用薬とする．軽症の高血圧では後者を第一選択薬としてもよい．Ca拮抗薬は，脳血管拡張，脳血流増加作用を有し，自動調節下限域を左方へ移動（改善）する作用も最近認められた[11]．一方，ACE阻害薬は，脳自動調節の改善作用，血管構築（リモデリング）の是正作用などが知られ，いずれも脳血管障害には有益な作用といえる．血管拡張性βブロッカー，あるいはα_1遮断薬もその副作用に注意して使うことができる．

■脳卒中再発予防とその他の治療

脳卒中再発のリスクは，高血圧以外にも年齢，糖尿病，心房細動，[redacted]酒，喫煙などがあげられ，抗血小板薬，抗凝血薬療法が行われている．欧米で行われた多施設臨床試験では，アスピリン，チクロピジンなどの抗血小板薬が，プラセボに比べて脳梗塞あるいはTIAの再発を有意に抑えている．脳卒中の病型別にみると，アテローム血栓性脳梗塞には抗血小板薬が再発予防として有用とする一方で，ラクナ梗塞にはわが国で無効（山口ら，1994年），あるいは国外でチクロピジンがminor strokeに有効（TASS，1989年）との報告もある．なお，実薬群に副作用（出血，消化器症状など）が出現するなど，その有用性については決定的ではない．

主幹動脈の狭窄閉塞例については，外科的治療（内膜切除術，血管吻合術，血管内外科治療）も二次予防として見逃せない．かつては欧米人に多い頸動脈病変が日本人にも確実にふえ，その原因として糖尿病が重要であることを著者らは経験している[12]．

■おわりに

脳血管障害診療の今日的課題は急性期治療である．これが患者の生命・機能予後を大きく左右し，ADL，QOLに影響を与え，寝たきりや痴呆へと連鎖する．しかし，究極の目標は脳卒中の発症（一次）予防であり，既発症者においては再発（二次）予防である．現時点では治療法に限界があり，有効な治療薬の開発を期待しつつ，今日可能なかぎりの予防をしなくてはならない．そのためには，医療従事者はもちろんのこと，国民病ともいえる脳血管障害が一般国民により正しく理解されるように努力しなくてはならない．

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